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(54) **Heterocyclic derivatives as platelet aggregation inhibitors**

(57) RS 3-Methyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyric acid and metabolically labile ester or amides thereof, and pharmaceutically acceptable salts thereof useful as an inhibitor of the binding of fibrinogen to glycoprotein IIb/IIIa.

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Description

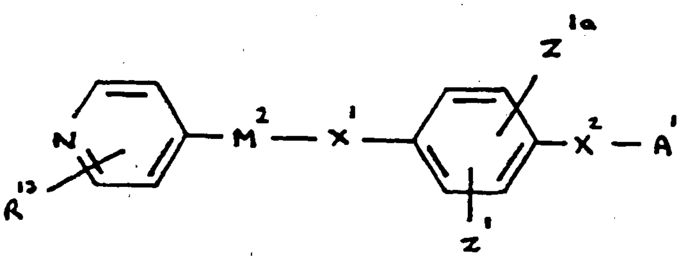
The present invention relates to a group of heterocyclic derivatives which inhibit cell adhesion (for example, platelet aggregation), to processes for their preparation and to pharmaceutical compositions containing them.

A variety of diseases involve cell adhesion during their development. For example, platelet aggregation is involved in the formation of blood thrombi, which can lead to diseases such as thrombosis, (eg stroke and thrombotic events accompanying unstable angina and transient ischaemic attack), myocardial infarction, atherosclerosis, thromboembolism and reocclusion during and after thrombolytic therapy.

It is widely believed that the platelet membrane glycoprotein IIb/IIIa (GPIIb/IIIa) mediates platelet aggregation. Adhesion molecules such as fibrinogen and von Willebrand Factor are believed to bind to GPIIb/IIIa sites on adjacent platelets and thereby cause them to aggregate. Other adhesion molecules which are known to bind to the GPIIb/IIIa are fibronectin, vitronectin and thrombospondin.

Surprisingly, as a result of random screening, the ability to inhibit platelet aggregation and to inhibit the binding of fibrinogen to GPIIb/IIIa has now been found to be possessed by certain heterocyclic derivatives containing a 4-[(4-pyridyl)piperazin-1-yl or related group.

According to one aspect, therefore, the present invention provides a compound of the general formula



I

wherein:

M^2 is **-NR**^{3}- in which **R**^{3} is hydrogen or (1-4C)alkyl; or is **-NR**^{4}**-D-TR**^{5}- in which

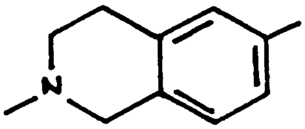
(i) **T** is N; **D** is CH_2CO; CH_2SO_2; (2-3C)alkylene optionally substituted by carboxy, (1-4C)alkoxycarbonyl or (1-4C)alkoxymethyl; and **R**^{4} and **R**^{5} together represent (2-3C)alkylene or CH_2CO, or each independently represents hydrogen or (1-4C)alkyl; or

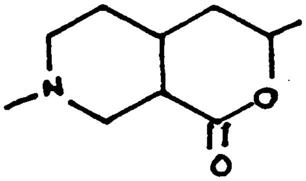
(ii) **T** is CH; **D** is CH_2CO, CH_2CH_2NH, (1-3C)alkylene optionally substituted by carboxy or (1-4C)alkoxycarbonyl, or (2-3C)alkyleneoxy; and **R**^{4} and **R**^{5} together represent (1-3C)alkylene; or

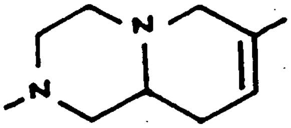
(iii) **R**^{4} and **-D-TR**^{5}- together form a (5-6C)alkenylene group.

X^1 is a bond or (1-4C)alkylene, (2-4C)alkenylene, (2-4C)alkynylene, (1-2C)alkylenephenylene, phenyleneoxy, phenyleneoxymethylene, phenylenecarbonyl, phenyleneCONH, (1-3C)alkylenecarbonyl, (1-2C)alkylenecarbonyl substituted by benzyl or p-hydroxybenzyl, methylidenepyrrolidin-1-ylacetyl, (1-2C)-alkylenecarbonyloxy, (1-2C)alkyleneCONH, (1-2C)alkyleneCONH(1-2C)alkyleneCO, (1-2C)alkyleneCONH(1-2C)alkyleneCONH, benzyl(1-2C)alkyleneCONH, (1-4C)alkyleneoxy, (1-2C)alkyleneoxy(1-2C)alkylene, (1-2C)alkyleneoxy(1-2C)alkylenecarbonyl, (1-3C) alkyleneCH(OH), and, when **M**^{2} is **-NR**^{4}**-D-TR**^{5}-, carbonyl, carbonyl(1-3C)alkylene, CONH, (1-2C)alkyleneNHCO and CONH(1-3C)alkylene, and when T is CH, oxy, oxy(1-3C)alkylene, oxy(1-2C)alkylenecarbonyl or oxy(1-2C)alkylenephenylene;

or **X**^{1} together with **M**^{2} may form a group of formula:







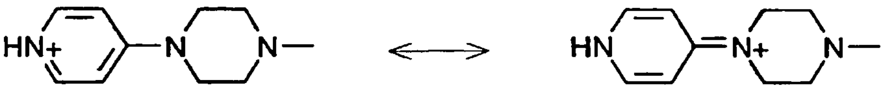
$\mathbf{Z^1}$ and $\mathbf{Z^{1a}}$ each independently represents hydrogen, hydroxy, halogeno, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkylthio, (2-4C)alkenylory, nitro, amino, (1-4C)alkylamino, (2-4C)alkanoylamino, cyano, (1-4C)alkylsulphonylamino; phenyl(1-2C)sulphonylamino, p-toluenesulphonylamino, or (1-4C)alkoxycarbonyl, or has one of the meanings given for $\mathbf{X^2}$-$\mathbf{A^1}$;

$\mathbf{X^2}$ is a bond or (1-4C)alkylene, (2-4C)alkenylene, oxy(1-4C)alkylene, oxy(5-6C)alkylene, oxy(2-4C)alkenylene, thio(1-3C)alkylene, SO_2(1-3C)alkylene, amino(1-3C)alkylene, SO_2NH(1-3C)alkylene, $NR^{21}CO$(1-2C)alkylene (where R^{21} represents hydrogen, (1-4C)alkyl or benzyl), $CONR^{21}$(1-2C)alkylene, in any of which the alkylene group may optionally be substituted by (2-4C)alkenyl; (2-4C)alkynyl; (1-4C)alkoxy; carboxy; (1-4C)alkoxycarbonyl; phenyl(1-4C)alkoxycarbonyl; phenyl(1-2C)alkylNHCO; carboxy(1-2C)alkyl; phenyl(1-2C)alkyl; phenylsulphonyl(1-2C)alkyl; pyridyl, phenyl; amino or a group of formula $NR^{12}XR^6$ in which **X** is SO_2, CO or CO_2; R^{12} is hydrogen or (1-4C)alkyl and $\mathbf{R^6}$ is (1-6C)alkyl, (6-10C)aryl, (6-10C)aryl(1-4C)alkyl, di(1-4C)alkylamino(1-4C)alkyl, morpholino(1-4C)alkyl, piperidino(1-4C)alkyl or N-(1-4C)alkylpiperidino(1-4C)alkyl.

$\mathbf{A^1}$ is carboxy or a metabolically labile ester or amide thereof; and

$\mathbf{R^{13}}$ is hydrogen, (1-4C)alkyl, (1-4C)alkoxy or halogen; and pharmaceutically acceptable salts thereof.

Without wishing to be bound by theory, it is believed that the nitrogen atom in the pyridyl group functions as a replacement for the strongly basic guanidine group in arginine. The function of the nitrogen atom which is attached to pyridyl in the group represented by M^2 is believed to be to contribute to the ability of the nitrogen atom in the pyridyl group to function as a base. For example a 4-(4-pyridyl)piperazin-1-yl group, the nitrogen atom in the piperazin-1-yl group is believed to contribute to the ability of the nitrogen atom in the pyridyl group to function as a base as shown below:-



Examples of values for -$\mathbf{NR^3}$- when $\mathbf{R^3}$ is hydrogen or (1-4C)alkyl are NH and methylimino.

Examples of values for -$\mathbf{NR^4}$-**D**-$\mathbf{TR^5}$- when **T** is N are 2-oxopiperazin-1,4-diyl, 2,6-dioxopiperazin-1,4-diyl, 1,1-dioxo-1,2,5-thiadiazin-2,5-diyl, piperazin-1,4-diyl, 2-carboxypiperazin-1,4-diyl, 3-carboxypiperazin-1,4-diyl, 2-methoxycarbonylpiperazin-1,4-diyl, 3-methoxycarbonylpiperazin-1,4-diyl, 2-methoxymethylpiperazin-1,4-diyl, 3-methoxymethylpiperazin-1,4-diyl and N-2-(N'-methylamino)ethyl(N-methyl)amino.

Examples of values for -$\mathbf{NR^4}$-**D**-$\mathbf{TR^5}$- when **T** is CH are pyrrolidin-3,1-diyl, 3-oxo-pyrrolidin-4,1-diyl 2-carboxypyrrolidin-4,1-diyl, 2-methoxycarbonylpyrrolidin-4,1-diyl, 2-ethoxycarbonylpyrrolidin-4,1-diyl, piperidin-3,1-diyl, piperidin-4,1-diyl, piperazin-2,4-diyl and morpholin-2,4-diyl.

All example of a group of formula -$\mathbf{NR^4}$-**D**-$\mathbf{TR^5}$- in which $\mathbf{R^4}$ and -**D**-$\mathbf{TR^5}$-together form a (5-6C)alkenylene group is 1,2,3,6-tetrahydropyridin-4,1-diyl.

Particularly preferred values for $\mathbf{M^2}$ are piperazin-1,4-diyl, piperidin-4,1-diyl and 2-oxo-piperazin-1,4-diyl.

Examples of values for $\mathbf{X^1}$ are a bond, methylene, ethylene, propylene, 1-methylethylene, ethenylene, ethynylene, methylenephenylene, phenyleneoxy, phenyleneoxymethylene, phenylenecarbonyl, phenyleneCONH, methylenecarbonyl, ethylenecarbonyl, 1-methylethylenecarboxyl, ethylidinecarbonyl, 2-propylidenecarbonyl, benzylmethylenecarbonyl, p-hydroxybenzylmethylenecarbonyl, methylidenepyrrolidin-1-ylacetyl, methylenecarbonyloxy, methyleneCONH, methyleneCONHmethyleneCONH, benzylmethyleneCONH, methyleneoxy, ethyleneoxy, propyleneoxy, butyleneoxy, methyleneoxymethylene, methyleneoxymethylenecarbonyl, methyleneCH(OH), and, when $\mathbf{M^2}$ is -$\mathbf{NR^4}$-**D**-$\mathbf{TR^5}$-, carbonyl, carbonylmethylene, carbonylethylene, CONH, methyleneNHCO, CONHmethylene, and when **T** is CH; oxy, oxymethylene, methyleneNHCO, oxymethylenecarbonyl and oxymethylenephenylene.

Particularly preferred values for $\mathbf{X}^1$ include a bond, methylenecarbonyl, ethylenecarbonyl ethylidinecarbonyl, carbonyl, carbonylethylene, methyleneoxy, ethyleneoxy and, when $\mathbf{M}^2$ is $\mathbf{-NR^4\text{-}D\text{-}TR^5\text{-}}$ and T is CH; oxy.

$\mathbf{Z}^1$ is preferably located ortho to $\mathbf{X}^2$; that is to say at the 2 or 6 position. Examples of phenylene groups optionally substituted by Z^1 and Z^{1a} are 1,4-phenylene, 2-methoxy-1,4-phenylene, 3-methoxy-1,4-phenylene, 2,6-dichloro-1,4-phenylene, 2,6-di-tert-butyl-1,4-phenylene, 2-carboxymethoxy-1,4-phenylene, 2-methoxycarbonylmethoxy-1,4-phenylene, 2-ethoxycarbonylmethoxy-1,4-phenylene, 3-methyl-1,4-phenylene, 2-methyl-1,4-phenylene, 3-methoxycarbonylmethoxy-1,4-phenylene, 2-allyl-1,4-phenylene, 2-propyl-1,4-phenylene, 2-nitro-1,4-phenylene, 3-ethoxycarbonylmethoxy-1,4-phenylene, 3-carboxymethoxy-1,4,phenylene, and 2-tert-butyloxycarbonylmethyloxy-1,4-phenylene.

Examples of values for Z^1 and Z^{1a} are hydrogen, hydroxy, chloro, fluoro and bromo, methyl, ethyl, propyl, t-butyl, allyl, methoxy, methylthio, allyloxy, nitro, cyano, methoxycarbonyl, carboxymethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy and tert-butyloxycarbonylmethoxy.

Examples of values for X^2 are a bond, methylene, ethylene, ethenylene, oxymethylene, 2-oxyethylene, 3-oxypropylene, 2-oxyprop-2-ylene, 4-oxybutylene, 5-oxypentylene, thiomethylene, aminomethylene, carboxamidomethylene, 2-carboxamidoethylene, 2-phenylethylidene, oxy(methoxycarbonyl)methylene, 1-(2-carboxyethyl)ethylene, 1-(benzyloxycarbonyl)ethylene, and groups of formula $CH_2CH(NR^{12}XR^6)$ such as 1-(butylsulphonylamino)ethylene $[CH_2CH(NHSO_2CH_2CH_2CH_2CH_3)]$, 1-(methylsulphonylamino)ethylene, 1-(benzylsulphonylamino)ethylene, 1-(p-toluenesulphonylamino)ethylene, 2-(butylsulphonylamino)ethylene, 2-(p-toluenesulphonylamino)ethylene, 3-oxy(1-(butylsulphonylamino)propylene), 2-carboxamido(2-phenyl)ethylene and 2-carboxamidopropylene.

Examples of values for R^{13} are hydrogen, methyl, methoxy and chloro. Preferably R^{13} is hydrogen.

Two preferred sub-groups of compounds of formula I may be identified. One consists of those compounds of formula I in which X^1 represents a bond. In this sub-group, X^2 preferably represents an oxy(2-4C)alkylene or oxy(5-6C)alkylene group, especially an oxypropylene group, optionally substituted on the alkylene group as defined hereinabove. The other consists of those compounds of formula I in which X^2 represents oxymethylene. In this sub-group, X^1 preferably represents methylenecarbonyl.

Examples of specifically preferred compounds are those of Examples 1, 2, 3, 4, 25, 26, 35, 36, 152, 153, 154 and 155 herein.

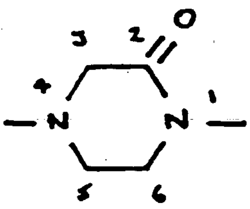
Examples of metabolically labile ester derivatives of a carboxy group are esters formed with alcohols such as (1-6C)alkanols, for example methanol, ethanol, propanol and isopropanol; indanol; adamantol; (1-6C)alkanoyloxy(1-4C)alkanols such as pivaloyloxymethyl; glycolamides; (S-methyl-2-oxo-1,3-dioxol-4-yl)methyl alcohol; and (1-4C)alkyloxycarbonyl(1-4)alkanols. It will be appreciated that compounds of formula I in which Z^1 is hydroxy may form internal esters.

Examples of metabolically labile amide derivatives of a carboxy group include amides formed from ammonia and amines such as (1-4C)alkylamine, for example methylamine, di(1-4C)alkyl amines, (1-4C)alkoxy(1-4C)alkylamines such as methoxyethyl amine, phenyl(1-2C)alkylamines such as benzylamine; and amino acids such as glycine or an ester thereof.

It will be appreciated that certain of the compounds of general formula I are in the form of enantiomers. It will be understood that the invention includes any enantiomer which has the property of inhibiting platelet aggregation and the binding of adhesion molecules to GPIIb/IIIa, whether present in a mixture with the other enantiomer (for example in a racemic mixture), or substantially free of the other enantiomer.

As used in this specification, the terms alkyl, alkylene, alkenylene or alkynylene include branched and unbranched groups. However, where specific terms are used, for example propyl, isopropyl or propylene, these indicate whether the group is branched or not. Diradicals, for example 2-oxo-piperazin-1,4-diyl, are numbered assuming that formula I is read from right to left with the group A^1 being at the right hand side, as depicted in formula I hereinabove.

Hence, for example, 2-oxo-piperazin-1,4-diyl signifies the group:-

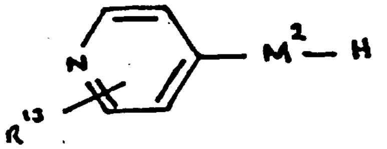


It will be appreciated that in this specification, the order of the two numbers immediately preceding the term "diyl" in the name of a diradical signifies the orientation of the diradical in a compound of formula I. Thus the first number signifies the position in the diradical closest to the group A^1.

Particular pharmaceutically acceptable salts include, for example, salts with acids affording physiologically acceptable anions, such as salts with mineral acids, for example a hydrogen halide (such as hydrogen chloride and hydrogen bromide), sulphuric acid or phosphoric acid, and salts with organic acids, for example trifluoroacetic acid. Other pharmaceutically acceptable salts include, for example salts with inorganic bases such as alkali metal and alkaline earth metal salts (for example sodium salts), ammonium salts, and salts with organic amines and quaternary bases forming physiologically acceptable cations such as salts with methylamine, dimethylamine, trimethylamine, ethylenediamine, piperidine, morpholine, pyrrolidine, piperazine, ethanolamine, triethanolamine, N-methylglucamine, tetramethylammonium hydroxide and benzyltrimethylammonium hydroxide.

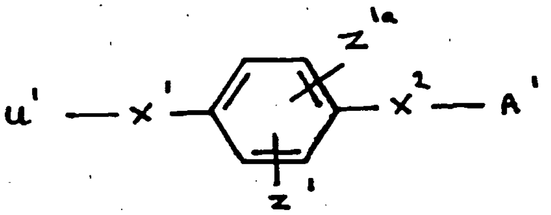
According to another aspect, the invention provides a process for preparing a compound of general formula I, or a metabolically labile ester or amide thereof, or a pharmaceutically acceptable salt thereof which comprises

(A) For a compound of formula I in which M^2 is NR^3 or $-NR^4-D-NR^5-$, reacting a compound of formula:



II

or an acid addition salt thereof with a compound of formula:



III

in which U^1 is a leaving atom or group.

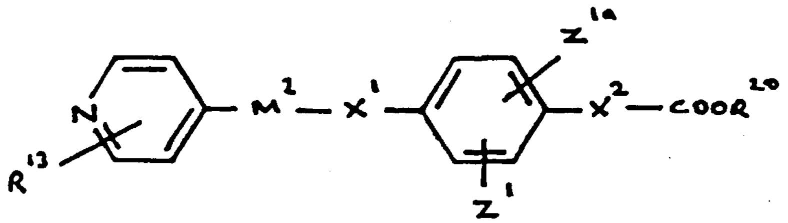
Examples of values for U^1 include halogen, such as chlorine or bromine, and hydrocarbylsulphonyloxy, such as methanesulphonyloxy and p-toluenesulphonyloxy. When the group in X^1 to which U^1 is attached is a carbonyl group, U^1 may also represent a hydroxy group or a reactive derivative thereof. Examples of reactive derivatives of a hydroxyl group include acyloxy groups such as acetyloxy, and groups formed in situ by reacting a compound of formula III in which U^1 is hydroxy with a peptide coupling reagent. Examples of peptide coupling reagents include carbodiimides such as 1,3-dicyclohexylcarbodiimide (DCC), preferably in combination with 1-hydroxybenzotriazole hydrate (HOBT).

Examples of acid addition salts include, for example the hydrochlorides.

The reaction may conveniently be effected at a temperature in the range of from -10 to 120 °C, preferably from 10 to 100 °C. Suitable solvents include, for example, ethers such as tetrahydrofuran, amides such as dimethylformamide, nitriles such as acetonitrile, halogenated hydrocarbons such as dichloromethane and alcohols such as ethanol or isopropanol.

In some circumstances, for example when an acid addition salt of a compound of formula II is used as starting material, or when the compound of formula II is relatively unreactive, the reaction may advantageously be performed in the presence of a base. Examples of suitable bases include tertiary amines, such as triethylamine, and alkali metal hydroxides, carbonates and bicarbonates, such as sodium or potassium hydroxide, carbonate or bicarbonate. When the compound of formula II is relatively unreactive a strong base such as an alkali metal hydride, for example potassium hydride, may conveniently be used.

(B) For a compound of formula I in which A^1 is carboxy, decomposing an ester of formula:



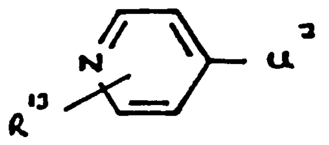
IV

in which R^{20} is a carboxyl protecting group.

R^{20} may be any conventional carboxyl protecting group that may be removed without interfering with other parts of the molecule. Examples of carboxyl protecting groups include (1-6C) alkyl groups (such as methyl, ethyl, propyl or t-butyl), phenyl and benzyl, the phenyl moiety in any of which may optionally bear 1 or 2 of halogeno, (1-4C)alkyl, (1-4C)alkoxy or nitro.

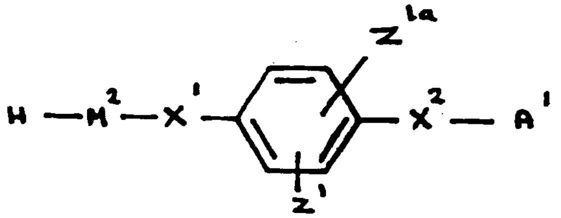
The decomposition may be carried out using any one or more of the conventional reagents and conditions known in the art for converting carboxylic esters into carboxylic acids. Thus, for example, the decomposition may conveniently be performed by base catalysed hydrolysis, for example by using an alkali metal hydroxide such as lithium, potassium or sodium hydroxide, or a tertiary amine such as triethylamine in the presence of water. The base catalysed hydrolysis may conveniently be performed in the presence of a solvent such as an alcohol, for example methanol or ethanol, or an ether such as tetrahydrofuran or dioxan. Alternatively the decomposition may be carried out by acid catalysed hydrolysis, for example using aqueous acetic acid or trifluoroacetic acid. The temperature is conveniently in the range of from -10 to 100°C, for example from 10 to 50°C. When the alcohol residue is t-butyl, this may also conveniently be removed by heating, for example at a temperature in the range of from 80 to 150°C, alone or in the presence of a suitable diluent such as diphenylether or diphenylsulphone. A benzyl group may conveniently be removed by catalytic hydrogenation, for example by hydrogenation in the presence of palladium on carbon at a temperature in the range of from -10 to 100°C in the presence of a solvent such as an alcohol, for example methanol or ethanol.

(C) Reacting a compound of formula:



VII

in which U^3 is a leaving atom or group, with a compound of formula:



VIII

or an acid addition salt thereof.

Examples of values for U^3 include halogen, such as chlorine or bromine, and cyano.

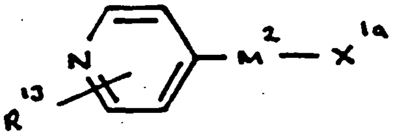
Examples of acid addition salts include, for example the hydrochlorides.

The reaction may conveniently be effected at a temperature in the range of from -10 to 120 °C, preferably from

10 to 100 °C. Suitable solvents include, for example, ethers such as tetrahydrofuran and dioxan, amides such as dimethylformamide, nitriles such as acetonitrile, halogenated hydrocarbons such as dichloromethane, alcohols such as ethanol and water.

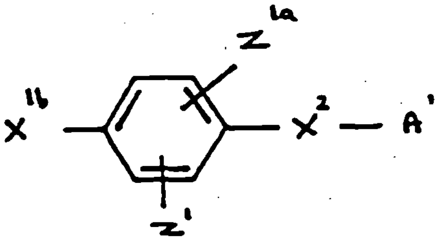
In some circumstances, for example when an acid addition salt of a compound of formula VIII is used as starting material, the reaction may advantageously be performed in the presence of a base. Examples of suitable bases include tertiary amines, such as triethylamine, and alkali metal hydroxides, carbonates and bicarbonates, such as sodium or potassium hydroxide, carbonate or bicarbonate.

(D) For a compound of formula I in which X^1 comprises a CONH group, reacting the appropriate carboxylic acid of formula:



IX

in which X^{1a} is a residue of a carboxylic acid group, or a reactive derivative thereof, with the appropriate amine of formula:



X

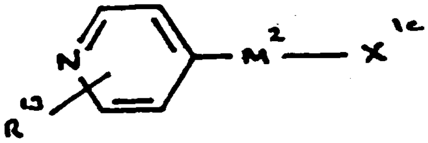
in which X^{1b} is a residue of an amine group.

Examples of values for X^{1a} are (1-2C)alkyleneCOOH, benzyl(1-2C)alkyleneCOOH and COOH. Examples of values for X^{1b} are H_2N and H_2N(1-3C)alkylene.

Examples of reactive derivatives of the compounds of formula IX include acyl halides such as the chlorides and bromides and groups formed in situ by reacting a residue of a carboxylic acid with a peptide coupling reagent, such as a carbodiimide, for example 1,3-dicyclohexylcarbodiimide, preferably in combination with 1-hydroxybenzotriazole hydrate (HOBT).

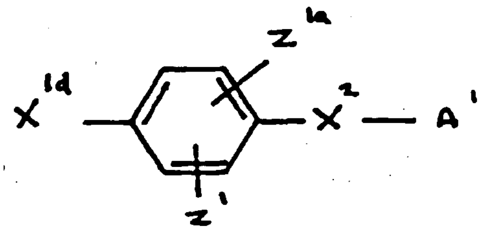
The reaction is conveniently performed at a temperature in the range of from 0 to 100°C. Suitable solvents include halogenated hydrocarbons such as dichloromethane, amides such as dimethylformamide and tertiary amines such as triethylamine.

(E) For a compound of formula I in which X^1 is (2-4C)alkenylene, reacting a compound of formula:



XI

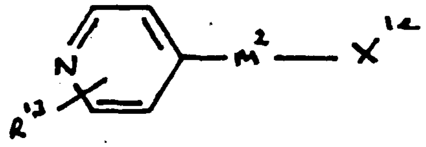
in which X^{1c} is an appropriate aldehyde-containing group with the appropriate Wittig reagent of formula:


XII

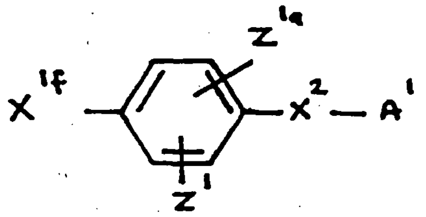
in which X^{1d} is a triarylphosphonylalkylene group such as triphenylphisphonylmethylene.

The reaction is conveniently performed at a temperature in the range of from -20 to 50°C, preferably from 0 to 25°C. Convenient solvents include ethers such as tetrahydrofuran, sulphoxides such as dimethylsulphoxide and aromatic hydrocarbons such as toluene.

(F) For a compound of formula I in which X^1 comprises an oxy (ether) link, reacting the appropriate compound of formula:


XIII

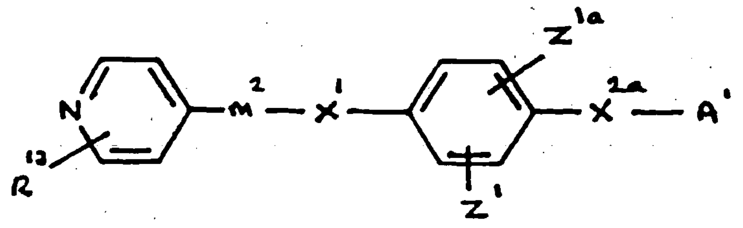
with the appropriate compound of formula:


XIV

in which one of X^{1e} and X^{1f} is a residue of an alcohol group, and the other is a residue of an alcohol group or a group containing a leaving atom or group.

When X^{1e} and X^{1f} both represent residues of alcohol groups, the reaction may conveniently be effected in the presence of a dehydrating agent such as diethyl azodicarboxylate-triphenylphosphine. Suitable solvents for the reaction include ethers such as tetrahydrofuran and amides such as dimethylformamide. The reaction is conveniently effected at a temperature in the range of from 0 to 50°C.

(G) For a compound of formula I in which X^2 is $CH_2CH(NHXR^6)$ reacting a compound of formula:


XV

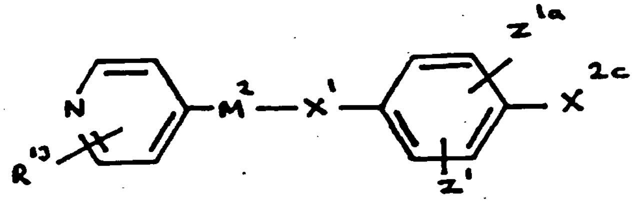
in which X^{2a} is $CH_2CH(NH_2)$, or an acid addition salt thereof, with a compound of formula

$R^6.X.U^4$ XVI

in which U^4 is a leaving atom or group.

Examples of values for U^4 include halogen, such as chlorine or bromine. Examples of acid addition salt include for example, the hydrochloride. The reaction may conveniently be effected at a temperature in the range of from -10 to 120°C preferably from 10 to 100°C. Suitable solvents include for example ethers such as tetrahydrofuran, amides such as dimethylformamide, nitriles such as acetonitrile, halogenated hydrocarbon such as dichloromethane and alcohols such as ethanol. The reaction is conveniently performed in the presence of a base, for example a tertiary amine such as triethylamine.

(H) For a compound of formula I in which X^2 represents oxyalkylene or oxyalkenylene, reacting a compound of formula



XVIII

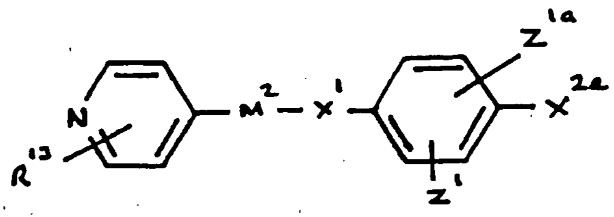
with the appropriate compound of formula

X^{2d}-A^1 XIX

in which X^{2c} is a hydroxy group, or a reactive derivative thereof (such as a halide), and X^{2d} is a hydroxyalkylene or hydroxyalkenylene group, or a reactive derivative thereof (such as a halide, for example a bromide).

The reaction is conveniently performed in the presence of a strong base, such as an alkali metal hydride, for example, sodium hydride. Suitable solvents include amides, such as dimethylformamide. The reaction is conveniently performed at a temperature in the range of from 0 to 100 °C.

(I) For a compound of formula I in which X^2 represents CONHalkylene, reacting a compound of formula



XX

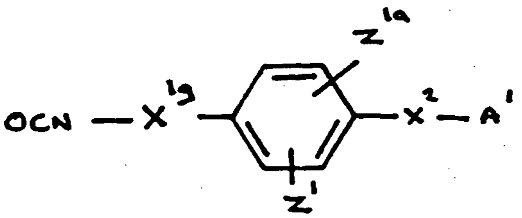
with the appropriate compound of formula

X^{2f}-A^1 XXI

in which X^{2e} represents a carboxyl group or a reactive derivative thereof (such as an acyl halide, for example an acyl chloride, or anhydride) and X^{2f} represents an aminoalkylene group, or an acid addition salt thereof (such as a hydrochloride).

Suitable solvents include halogenated hydrocarbons such as dichloromethane, amides such as dimethylformamide and tertiary amines, such as triethylamine. The reaction is conveniently performed at a temperature in the range of from 0 to 100 °C.

(J) For a compound of formula I in which X^1 represents CONH or CONHalkylene, reacting a compound of formula II with a compound of formula

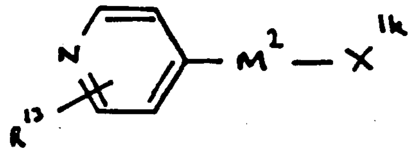


XXII

in which X^{1g} is a bond or an alkylene group.

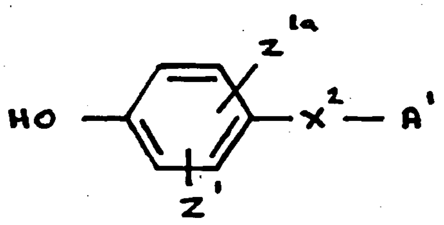
The reaction is conveniently performed at a temperature in the range of from 0 to 100 °C. Suitable solvents include halogenated hydrocarbons, such as dichloromethane.

(K) For a compound of formula I in which X^1 is (1-2C)alkylenecarbonyloxy, reacting a compound of formula



XXVI

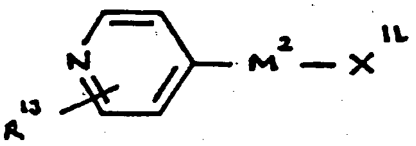
in which X^{1k} represents (1-2C)alkylenecarboxy or a reactive derivative thereof, with a compound of formula



XXVII

The reaction is conveniently performed at a temperature in the range of from 0 to 100°C. Suitable solvents include halogenated hydrocarbons such as dichloromethane.

(L) For a compound of formula I in which X^1 represents (1-3C)alkylenecarbonyl, reacting a compound of formula



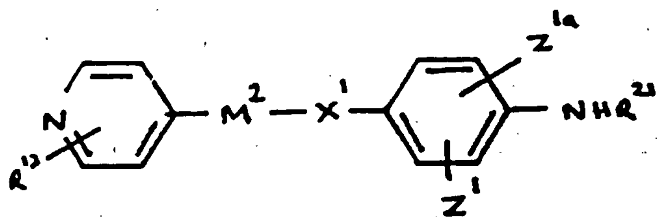
XXVIII

in which X^{11} represents a (1-3C)alkylenecarboxyl group, or a reactive derivative thereof, with a compound of formula VI in the presence of a Lewis acid.

Example of suitable Lewis acids include aluminium trichloride. Examples of reactive derivatives of compounds of formula XXVIII include the halides, such as the chlorides.

The reaction is conveniently performed at a temperature in the range of from -10 to 50°C. Suitable solvents include halogenated hydrocarbons, such as dichloromethane.

(M) For a compound of formula I in which X^2 represents $NR^{21}CO$(1-2C)alkylene, reacting a compound of formula



XXIX

with a compound of formula

X^{2h}-A XXX

in which X^{2h} represents a carboxy(1-2C)alkyl group, or a reactive derivative thereof.

Examples of reactive derivatives of compounds of formula XXX include halides, such as chlorides, and anhydrides.

The reaction is conveniently performed at a temperature in the range of from 0 to 100°C. Suitable solvents include amides such as dimethylformamide.

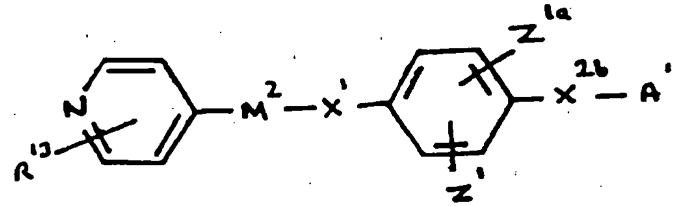
Certain compounds of formula I may be converted into other compounds of formula I using conventional methods. For example, a compound of formula I in which X^1 is a (2-4C)alkylene group may be prepared by hydrogenating a corresponding compound of formula I in which X^1 represents a (2-4C)alkenylene group. The hydrogenation may be effected, for example, in the presence of palladium on charcoal and in a suitable solvent such as an alcohol, for example ethanol. A compound of formula I in which X^1 is (1-3C)alkyleneCH(OH) may be prepared by reducing a corresponding compound of formula I in which X^1 is (1-3C)alkylenecarbonyl. The reduction may be effected, for example, using an alkali metal borohydride such as sodium borohydride.

The intermediates used in the aforementioned processes are known or may be prepared by methods analogous to those known for the preparation of known compounds.

Thus, the compounds of formula IV may be prepared by methods analogous to processes (A) and (C) to (G) herein, but starting from the appropriately protected starting materials. It will be appreciated that some compounds of formula IV are compounds according to the invention.

The compounds of formula II in which M^2 is a 2-oxopiperazin-1,4-diyl group may be prepared by reacting piperazinone with a compound of formula VII.

The compounds of formula XV may be prepared by deprotecting a corresponding compound of formula:



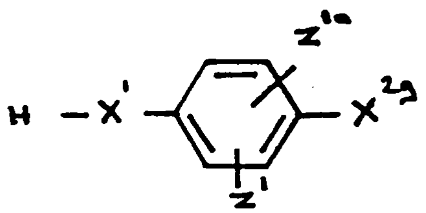
XVII

wherein X^{2b} is $CH_2CH(NHR^{11})$ and R^{11} is an amine protecting group.

Examples of amine protecting groups include oxycarbonyl groups such as benzyloxycarbonyl. A benzyloxycarbonyl group may conveniently be removed, for example, by hydrogenation in the presence of a palladium carbonyl such as palladium on charcoal.

The compounds of formula XVII may be prepared by a method analogous to the preparation of a compound of formula I, but starting from the appropriate starting material. For example, if a compound of formula XVII in which X^1 is methyleneoxy is desired, this may be prepared by a method analogous to process (F) herein, starting with a compound of formula XIII and the appropriate N-protected derivative of tyrosine.

The compounds of formula XVIII may be prepared by reacting a compound of formula VII with a compound of formula



XXIII

in which X^{2g} is a hydroxy group or a protected derivative thereof (for example a methoxy group), followed if necessary by the removal of any protecting group, (for example by treatment with hydrobromic acid) and, if desired, conversion of the hydroxy group into a reactive derivative thereof by a known method.

Many of the intermediates, for example compounds of formulae XV, XVII and XVIII, and the compounds of formula II and VIII in which M^2 is 2-oxopiperazin-1,4-diyl are novel and form further aspects of this invention.

The compounds of formula I may be converted into pharmaceutically acceptable salts and/or metabolically labile esters or amides thereof by methods well known in the art. For example, a pharmaceutically acceptable salt may be formed by reacting a compound of formula I with an acid capable of affording a physiologically acceptable anion, or a base capable of affording a physiologically acceptable cation. A pharmaceutically acceptable metabolically labile ester, or amide may be formed respectively by esterifying a compound of formula I using a conventional technique, or reacting an acid, or a reactive derivative thereof with the appropriate amine.

The ability of the compounds of formula I to inhibit platelet aggregation may be demonstrated using a standard test (a) based on that described by Born (Nature, 1962, 194, 927-929) and involving:

(i) aggregating human, citrated, platelet-rich plasma by addition of adenosine diphosphate so as to generate a dose-response curve;
(ii) generating a dose-response curve for ADP stimulated platelet aggregation in the presence of increasing amounts of a test compound (generally in the range 10^{-5}M to 10^{-10}M); and
(iii) calculating a pA_2 value indicating potency of platelet aggregation inhibition for the test compound, averaged over several concentrations, from the calculated 50% response value for ADP aggregation in the presence and absence of the test compound.

Test (a) may be modified so as to assess the effects of a test compound ex vivo on the aggregation of human blood platelets after administration of the test compound to a laboratory animal, such as a rat, rabbit, guinea pig, mouse or dog. For example, groups of four male, fasted Alderley Park Wistar rats are orally dosed with a test compound or appropriate vehicle, and at suitable time intervals (1,3,5 and 8 hours after dosing) animals are anaesthetised with fluothane and bled by heart puncture. Blood is collected into 3.2% citrate (1 part to 9 parts whole blood) and platelet poor plasma (ppp) prepared by centrifugation (4500 x g for 10 min).

Human blood is collected into 3.2% trisodium citrate (1 part to 9 parts whole blood) and centrifugated (200 x g for 15 min) to produce platelet rich plasma (prp).

Equal volumes (125µl) of rat ppp and human prp are mixed together, ADP added, and the whole incubated (37°C) and stirred (900 rpm) in a BioData platelet aggregometer. Aggregation is induced with ADP and agonist EC_{50} values calculated for human prp/rat ppp mixtures from animals dosed with test compound or vehicle. A mean concentration ratio (concentration of ADP required to cause a 50% aggregation response in human prp/rat ppp mixtures from animals dosed with antagonist, divided by the concentration of ADP to cause 50% aggregation in human prp/rat ppp mixtures from animals dosed with vehicle) is calculated at each time point.

The ability of the compounds of formula I to inhibit binding of fibrinogen to GPIIb-IIIa may be demonstrated using the following standard test (b) involving:

(i) Preparation of human platelet lysates.
Platelet rich plasma (PRP) is harvested by centrifugation (1000 rpm, 15 mins) of whole blood anticoagulated with acid citrate dextrose (trisodium citrate 85mM, citric acid 70mM, d-glucose 110mM) 1 part to 6 parts blood. Prostacyclin (PGI_2, 1µM) is added to the PRP before centrifugation (2400rpm, 15mins) and the resulting pellet is resuspended in modified Tyrodes' solution (NaCl 130mM, KCl 26mM, $NaHCO_3$ 12mM, NaH_2PO_4 0.5mM, $MgCl_2$ 1mM, $CaCl_2$ 20mM, Glucose 12mM, HEPES 5mM) containing bovine serum albumin 3.5g/L, PGI2 1µM and hirudin 0.5U/ml. The platelet suspension is centrifuged (2400rpm, 15mins) and the resultant pellet resuspended in 500µl of lysis buffer (octyl glucoside 50mM, HEPES 10mM, NaCl 150mM, $CaCl_2$ 1mM, $MgCl_2$ 1mM, PMSF 1mM, NEM 10mM, leupeptin 0.1mM), agitated at 4°C for 15 minutes then centrifuged at 24000rpm, 15 mins. The supernatant

is stored at 4°C and the pellet re-suspended in 500µl of lysis buffer. The centrifugation process is repeated a further 3 times, the pooled supernatants being stored at -70°C.

(ii) Receptor purification.
Glycoprotein IIb/IIIa is isolated from human platelet lysates using a 2ml peptide (KYGRGDS) coupled CNBr activated Sepharose affinity column. A 1.5ml volume of platelet lysate is placed on the column and allowed to stand overnight at 4°C. Buffer (30mls, octyl glucoside 25mM, HEPES 10mM, NaCl 150mM, CaCl2 1mM, MgCl2 1mM, PMSF 1mM, NEM 10mM, leupeptin 0.1mM) is passed through the column and 2ml fractions are collected throughout. GPIIb/IIIa is eluted with 12mls of buffer containing HHLGGAKQAGDV (2mg/ml, pH 7.5), the column is washed using 4mls buffer and the remaining GPIIb/IIIa eluted using 12mls buffer containing GRGDSPG (1mg/ml pH 7.5). The column is finally washed using 20mls of buffer and can be used for up to three such preparations. Fractions containing GPIIb/IIIa are identified using gel electrophoresis and immunoblotting, pooled and stored at -70°C.

(iii) GPIIb/IIIa ELISA
96 well microtitre plates are coated with 100µl purified human platelet fibrinogen receptor (GPIIb/IIIa) diluted in coating buffer (Tris-HCl 20mM, NaCl 150mM, $CaCl_2$ 1mM, pH 7.4) and left overnight at 4°C. The plates are washed using washing buffer (Tris-HCl 50mM, NaCl 100mM, $CaCl_2$ 2mM, pH 7.4) and non-specific binding blocked by the addition of 200µl 2% BSA (2 hours, 30°C). The plates are washed prior to incubation (2 hours, 30°C) with 100µl biotinylated fibrinogen (10nm) containing either vehicle or test compound. The plates are washed, incubated with streptavidin (5µg/ml, 1 hour, ambient temperature), then washed again before the addition of 100µl biotinylated horse radish peroxidase (0.1µg/ml, 1 hour, ambient temperature). The plates are then washed and equal volumes of peroxidase substrate (3, 5, tetramethyl benzidine 0.4g/l) and H_2O_2 (0.02%) are mixed together immediately before addition of 150µl to each well. Colour is allowed to develop for 10-15 mins before optical densities are read at 650nM.

Abbreviations

PMSF	Phenylmethylsulphonylfluoride
HEPES	(N-[2-Hydroxyethyl]piperazine-N-[2-ethanesulphonic acid]
NEM	N-ethyl maleimide

The concentration of compound required to cause 50% inhibition of biotinylated fibrinogen binding is calculated and expressed as a pIC_{50} ($-\log(IC_{50})$).

In general, test compounds showing activity in this test show a pIC_{50} of greater than about 4.0.

The effects of each of the compounds of formula I exemplified herein in the above tests are given in the table below. Where a range of values is given, the compound has been tested more than once. A dash (-) signifies that a compound has not been tested.

TABLE OF BIOLOGICAL TEST RESULTS

Example	Test (a)	Test (b)	Example	Test (a)	Test (b)
1	6.5-6.8	5.8-6.4	34	5	4.8
2	7.1-7.3	7.6	35	7.5	6.7
3	6.3	6.6	36	7.9-8.6	8.1
4	8.9	9.1	37	6.9	6.5
5	6.0	6.0	38	7.5	7.7
6	7.2	7.6	39	5.7	6.6
7	6.3	5.2-5.4	40	8.6	8.5
8	6.5	7.1	41	6.5	7.9
9	4.9	4.3	42	5.1	6.3
10	5.7	6.0	43	6.8	6.6
11	5.7	4.4	44	7.9	8.5
12	6.3	7.2	45	4.8	6.7
13	5.3	4.4-4.8	46	6.3	7.9
14	5.1	<4	47	4.4	5.7
15	5.6	5.9	48	7.2	7.7
16	6.8	6.7	49	5.8	6.6
17	7.4	7.7	50	5.4	6.7
18	6.3	6.5	51	5.6	7.2
19	6.4	6.9	52	9	8.6
20	8.7	8.7	53	7.4	8.7
21	6.4	7.2	54	8	8.5
22	8.7	9.0	55	6.8	6.7
23	5.6	6.7	56	5.7	7.1
24	7.5	8.7	57	7.9	8.5
25	6.0-6.1	<4	58	6.5	8.6
26	7-7.9	7.6-8.4	59	5	5.1
27	5	<4	60	7.1	8.4
28	5.8	5.9	61	5.4	5.5
29	4.8	<4	62	7.6	8.5
30	5.5	4.8	63	5.4	6.6
31	7.6	7.6	64	4.4	5.4
32	5.5	4.4	65	6.3	7.5
33	7.2	7.5	66	5.7	5.6

Example	Test (a)	Test (b)	Example	Test (a)	Test (b)
67	6.7	6.4	101	6.1	7.8
68	5.4	4.3	102	4.9	4.3
69	5.9	5.4	103	4.7	6.2
70	6.2	5.4	104	6.4	6.6
71	6.0	7.0	105	8.1	7.2-7.4
72	6.8	7.8	106	5.9	4.7
73	5.8	6.7	107	5.8	6.5
74	6.8	6.3	108	6.6	6.7
75	7.9	6.5	109	6.1	6.4
76	<4	5.4	110	4.4	5.0
77	4.6	4.5	111	5.2	4.3
78	4.2	4.5	112	5.9	6.7
79	4.5	<4	113	6.4-6.8	8.0-8.3
80	6.9	5.6	114	5.9	6.2
81	7.2	5.5	115	6.7	8.0
82	5	4.9	116	5.8	4.1
83	6.6	5.4	117	5.5	6.0
84	5.8	6.3	118	4.8	5.4
85	5.3	5.3	119	5.5	-
86	5.0	4.5	120	6.5	-
87	5.3	5.3	121	4.8	-
88	5.5	5.3	122	6.0	-
89	5.1	5.2	123	5.9	6.5
90	6.4	6.2	124	4.2	4.7
91	7.3	7.5	125	<4	5.4
92	4.7	4.7	126	<4	6.6
93	6.5	6.5	127	4.4	6.6
94	6.2	5.4	128	6.3	-
95	7.0	7.0	129	7.9	8.4
96	5.5	<4	130	4.3	<4
97	4.7	5.8	131	-	-
98	6.5	7.1	132	7.2	8
99	6.2	7.0	133	7.1	8.9
100	6.3	5.7	134	6.6	-

Example	Test (a)	Test (b)
135	6.6	8.0
136	6.5	6
137	6.5	-
138	6.7	-
139	6.5	-
140	5.8	6.8
141	7.1	-
142	6.7	6.3
143	-	-
144	6.9	-
145	5.7	-
146	6.5	-
147	6.0	-
148	7.5	-
149	5.5	-
150	6.8	-
151	6.1	-
152	7.6	-
153	8.2	-
154	6.5	-
155	8.0	-
156	-	-

In general, it has been found that compounds of formula I in which A^1 is carboxy show a higher level of activity in test (a), and test (b) than those in which A^1 is an ester group. However, the compounds in which A^1 is an ester group have often been found to show a higher level of activity than those where A^1 is carboxy in test (a) when the test is modified to assess the activity of test compounds on oral administration

For example, the compound described in Example 1 hereinafter has been found to give a **pA_2** of 6.5-6.8 in test (a) and a pIC_{50} of 5.8 -6.4 in test (b), whereas the compound of Example 2 has been found to give a pA_2 of 7.1-7.3 in test (a) and a pIC_{50} of 7.6 in test (b). However, the compound of Example 1 has been found to be active for up to 12 hours when dosed orally to dogs at 5mg/kg. Without wishing to be bound by theory it is accordingly believed that the compounds of formula I in which A^1 represents an ester group function as a pro-drugs for compounds of formula I in which A^1 is a carboxyl group.

As stated previously, the compounds of formula I may be used in the therapy or prevention of diseases in which cell adhesion (especially platelet aggregation) is involved, for example venous or arterial thrombosis (e.g. pulmonary embolism, stroke and thrombotic events accompanying unstable angina and transient ischaemic attack), myocardial infarction, atherosclerosis, thromboembolism and reocclusion during and after thrombolytic therapy. The compounds may also be useful for the prevention of reocclusion and restenosis following percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft. It will also be appreciated that the compounds may be useful in the treatment of other diseases mediated by binding of adhesion molecules to GPIIb/IIIa, for example cancer.

According to another aspect, therefore, the invention provides a method of inhibiting platelet aggregation in a warm-blooded mammal requiring such treatment, which comprises administering an effective amount of a compound of formula I, or a metabolically labile ester or amide thereof, or a pharmaceutically acceptable salt.

According to yet another aspect, the invention provides a method of inhibiting binding of fibrinogen to GPIIb/IIIa in a warm-blooded animal requiring such treatment, which comprises administering an effective amount of a compound of formula I, or a metabolically labile ester or amide thereof, a pharmaceutically acceptable salt thereof.

According to a further aspect, the invention provides the use of a compound of formula I, or a metabolically labile ester or amide thereof or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the prevention or treatment of a disease involving platelet aggregation.

According to yet another aspect, the invention provides the use of a compound of formula I or a metabolically labile ester or amide thereof or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or treatment of a disease involving binding of fibrinogen to GPIIb/IIIa.

In general, a compound of formula I will be administered for this purpose by an oral, rectal, topical, intravenous, subcutaneous, intramuscular or inhalation route, so that a dose in the range of from 0.01 to 50 mg/kg body weight will be given, depending upon the route of administration, the age and sex of the patient, and the severity of the condition to be treated.

The compounds of formula I will generally be used in the form of a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinabove , together with a pharmaceutically acceptable diluent or carrier. Such a composition is provided as a further feature of the invention and may be in a variety of dosage forms. For example, it may be in the form of tablets, capsules, solutions or suspensions for oral administration; in the form of cream or ointments or a transdermal (skin) patch for topical administration; in the form of a suppository for rectal administration; in the form of a sterile solution or suspension for administration by intravenous or intramuscular injection; in the form of an aerosol or a nebuliser solution or suspension, for administration by inhalation; and in the form of a powder, together with pharmaceutically acceptable inert solid diluents such as lactose, for administration by insufflation. Depending upon the route of administration, the composition may comprise, for example, for 0.1 to 99.9% by weight of a compound of formula I.

The pharmaceutical compositions may be obtained by conventional procedures using pharmaceutically acceptable diluents and carriers well known in the art. Tablets and capsules for oral administration may conveniently be formed with an enteric coating, for example comprising cellulose acetate phthalate, to minimise contact of the active ingredient of formula I with stomach acids.

The compounds according to the invention may be co-adminstrated or co-formulated with one or more agents known to be of value in diseases or conditions intended to be treated; for example a known platelet aggregation inhibitor (e.g. aspirin, a thromboxane antagonist or a thromboxane synthase inhibitor), hypolipidemic agent, anti-hypertensive agent, thrombolytic agent (such as streptokinase, urokinase, prourokinase, tissue plasminogen activator and derivatives thereof), beta-adrenergic blocker or a vasodilator may usefully also be present in a pharmaceutical composition of the invention for use in treating a heart or vascular disease or condition.

In addition to their use in therapeutic medicine, the compounds of formula I are also useful as pharmacological tools in the development and standardisation of test systems for the evaluation of the effects of adhesion molecules in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents. The compounds of formula I may also be used because of their platelet aggregation inhibitory properties in helping to store blood and to maintain the viability of blood and blood vessels in warm-blooded animals (or parts thereof) under-going artificial extracorporeal circulation, for example during limb or organ transplants. When used for this purpose a compound of formula I, or a physiologically acceptable salt thereof, will generally be administered so that a steady state concentration in the range, for example, 0.1 to 10 mg. per litre is achieved in the blood.

The invention will now be illustrated by the following non-limiting Examples in which unless otherwise stated:-

(i) concentrations and evaporations were carried out by rotary evaporation in vacuo;
(ii) operations were carried out at ambient temperature, that is in the range 18-26°C;
(iii) column chromatography was carried out on silica (Merck Art. 9385) available from E Merck and Co., Darmstadt, Germany; and on neutral alumina (ICN Alumina N, Akt. III or IV) available from ICN Biomedicals GmbH, D-3440 Eschwege, Germany;
(iv) yields are given for illustration only and are not necessarily the maximum attainable by diligent process development;
(v) proton NMR spectra were normally determined at 200 MHz or 250 MHz in dimethylsulphoxide-d_6 using tetramethylsilane (TMS) as an internal standard, and are expressed as chemical shifts (delta values) in parts per million relative to TMS using conventional abbreviations for designation of major peaks: s, singlet; m, multiplet; t, triplet; br, broad; d,doublet; and
(vi) ether refers to diethyl ether, THF to tetrahydrofuran, DMF to N,N-dimethylformamide, DMSO to dimethylsulphoxide, TFA to trifluoroacetic acid; HOBT to 1-hydroxybenzotriazole; and NBA to m-nitrobenzylalcohol.
(vii) Drying with PS paper refers to the use of Whatmans PS phase separating paper.

EXAMPLE 1: Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenoxyacetate.

A solution of methyl 4-bromoacetylphenoxyacetate (4.3g) in acetonitrile (50ml) was added dropwise over 40 minutes to a stirred solution of 1-(4-pyridyl)piperazine (4.9g) in acetonitrile (100ml). Stirring was continued for a further 1.5 hours, then the solution was filtered and the filtrate evaporated in vacuo. The solid residue was triturated with water (50ml), then dried and suspended in methylene chloride (50ml). The suspension was then filtered and the filtrate concentrated to a small volume. Purification by flash chromatography on neutral alumina eluting first with dichloromethane, then 0.5% v/v methanol/dichloromethane and finally 1% v/v methanol/dichloromethane gave the title compound, 1.93g, as a solid: m.p. 150 - 152°C; NMR(d^{6}DMSO) δ 8.14(2H,d), 7.98(2H,d), 7.03(2H,d), 6.78(2H,d), 4.90(2H,s), 3.83(2H,s), 3.72(3H,s), 3.34(4H,bt), 2.65(4H,bt); m/e 370 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4$: C, 65.0; H, 6.3; N, 11.4. found: C, 65.2; H, 6.4; N, 11.3%.

EXAMPLE 2: 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenoxyacetic acid

A stirred solution of the product of Example 1 (550mg) in methanol (10ml) was treated with a M sodium hydroxide solution (1.65ml) and stirring continued for a further 2 hours. The mixture was diluted with water (10ml) and the resulting solution concentrated in vacuo. Water (20ml) was added and then a M hydrochloric acid solution (1.65ml). On cooling to 4°C, a solid precipitated. This mixture was concentrated in vacuo, the solid collected and washed with ice-water, then dried to give the title compound, 320mg, as a solid: m.p. 294-296°C; **NMR** (d^{6}DMSO+TFA) δ 8.34(2H,d), 7.95(2H,d), 7.26(2H,d), 7.10(2H,d), 5.06(2H,s), 4.82(2H,s), 4.06(4H,bs), 3.52(4H,bs); m/e 356$(M+H)^+$; calculated for $C_{19}H_{21}N_3O_4$: C, 64.2; H, 6.0; N, 11.8. found: C, 64.1; H, 6.1; N, 11.6%.

EXAMPLE 3: Dimethyl 2,2'-[4-[2-[4-(4-pyridyl)piperazin-1-yl)acetyl]phenylene-1,2-dioxy]diacetate.

A solution of dimethyl 2,2'-[4-bromoacetyl]phenylene-1,2-dioxy)diacetate (3.0g) in acetonitrile (15ml) was added dropwise over 30 minutes to a stirred solution of 1-(4-pyridyl)piperazine (2.6g) in acetonitrile (75ml) and the mixture stirred overnight. The mixture was then filtered and the filtrate evaporated to give an oil. Purification by flash chromatography on silica eluting first with 2.5% v/v methanol/dichloromethane then 5% v/v methanol/dichloromethane gave a solid. Trituration with ether gave the title compound, 0.95g, as a solid: m.p. 81 - 83°C; NMR (d^{6}DMSO) δ 8.14(2H,d), 7.67(1H,dd), 7.52(1H,d), 7.03(1H,d), 6.80(2H,d), 4.94(2H,s), 4.88(2H,s), 3.81(2H,s), 3.69(6H,s), 3.29(4H,t), 2.60(4H,t); m/e 458 $(M+H)^+$; calculated for $C_{23}H_{27}O_7N_3$. 0.25H_2O: C, 59.8; H, 6.0; N, 9.1. found C, 59.7; H, 6.2; N, 8.8%.

The starting material was prepared as follows:-

(i) Methyl bromoacetate (19.1ml) was added dropwise to a stirred mixture of 3,4-dihydroxyacetophenone (12.6g) and anhydrous potassium carbonate (27.5g) in acetone (250ml). Stirring was continued for 16 hours when the mixture was filtered and the solvent removed in vacuo. The residue after trituration with ether gave dimethyl 2,2'-([4-acetyl]phenylene-1,2-dioxy)diacetate, 13.1g, as an off-white solid: m.p. 101-102°C; NMR (d^{6}DMSO) δ 7.60(1H,dd), 7.41(1H,d), 7.02(1H,d), 4.94(2H,s), 4.89(2H,s), 3.71(6H,s), 2.50(3H,s); m/e 297$(M+H)^+$; calculated for $C_{14}H_{16}O_7$: C, 56.8; H, 5.4. found: C, 56.4; H, 5.5%.

(ii) A solution of bromine (2.27ml) in chloroform (10ml) was added dropwise over 15 minutes to a stirred solution of the product of step (i) (12.9g) in chloroform (40ml) at 30°C. The mixture was then stirred for 2 hours at ambient temperature when the solvent was removed in vacuo. The resulting waxy solid, on trituration with ethanol, gave dimethyl
2,2'-([4-bromoacetyl]phenylene-1,2-dioxy)diacetate, 11.5g, as a cream solid: m.p. 76-78°C; NMR(d^{6}DMSO) δ 7.66(1H,dd), 7.47(1H,d), 7.06(1H,d), 4.96(2H,s), 4.90(2H,s), 4.62(2H,s), 3.71(6H,s); m/e 375/377 $(M+H)^+$, 1 Br pattern.

EXAMPLE 4: 2,2'-[4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenylene-1,2-dioxy]diacetic acid.

A stirred solution of the product of Example 3 (300mg) in methanol (4ml) was treated with a M sodium hydroxide solution (1.31ml) and the mixture stirred for 1 hour. The mixture was diluted with water (10ml) and the resulting solution concentrated to about 7ml when a M hydrochloric acid solution (1.31ml) was added. On cooling to 4°C the solid formed was collected, then washed with ice-water and dried to give the title compound, 120mg, as a white solid: m.p. 180-184°C (dec); NMR(d^{6}DMSO) δ 8.16(2H,d), 7.61(2H,t), 6.93(1H,d), 6.87(2H,d), 4.73(2H,s), 4.68(2H,s), 3.77(2H,s), 3.44(4H,bt), 2.58(4H,bt); m/e 430 $(M+H)^+$; calculated for $C_{21}H_{23}O_7N_3$. 0.75H_2O: C, 56.9; H, 5.5; N, 9.5. found C, 57.0; H, 5.6; N, 9.3%.

EXAMPLE 5: Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-2-methoxyphenoxyacetate

A solution of methyl 4-bromoacetyl 2-methoxyphenoxyacetate (1.27g) in acetonitrile (10ml) was added dropwise over 15 minutes to a stirred solution of 1-(4-pyridyl)piperazine (1.30g) in acetonitrile (30ml). After stirring overnight the liquors were decanted from the solid residue, then concentrated in vacuo. Purification by flash chromatography on silica, eluting with dichloromethane then 5% v/v methanol/dichloromethane gave a solid. Trituration with ether gave the title compound, 420mg: m.p. 110 - 112°C; NMR (d^6DMSO) δ 8.14(2H,d), 7.65(1H,dd), 7.55(1H,d), 6.97(1H,d), 6.80(2H,d), 4.90(2H,s), 3.87(5H,s), 3.72(3H,s), 3.33(4H,t), 2.62(4H,t); m/e 400(M+H)$^+$; calculated for $C_{21}H_{25}N_3O_5$: C, 63.1; H, 6.3; N, 10.5. found: C, 62.9; H, 6.3; N, 10.4%.

EXAMPLE 6: 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]-2-methoxyphenoxyacetic acid

In a similar manner to Example 2, but starting from the product of Example 5, the title compound was prepared in 47% yield: m.p. 218 - 224°C; NMR(d^6DMSO) δ 8.16(2H,d), 7.65(1H,dd), 7.53(1H,d), 6.92(1H,d), 6.85(2H,d), 4.73(2H,s), 3.86(2H,s), 3.82(3H,s), 3.36(4H,t), 2.63(4H,t); m/e 386(M+H)$^+$; calculated for $C_{20}H_{23}N_3O_5$. H_2O: C, 59.5; H, 6.2; N, 10.4. found: C, 59.5; H, 5.9; N, 10.1%.

EXAMPLE 7: Methyl 4-[3-[4-(4-pyridyl)piperazin-1-yl]propanoyl]phenoxyacetate

In a similar manner to Example 3, but starting from methyl 4-[3-chloropropanoyl]phenoxyacetate was prepared the title compound in 65% yield: m.p. 93 - 95°C; NMR (d^6DMSO) δ 8.14(2H,d), 7.96(2H,d), 7.04(2H,d), 6.81(2H,d), 4.92(2H,s), 3.71(3H,s), 3.29(4H,t), 3.17(2H,t), 2.72(2H,t), 2.51(4H,t); m/e 384 (M+H)$^+$; calculated for $C_{21}H_{25}N_3O_4$ C, 65.8; H, 6.6; N, 11.0. found C, 65.6; H, 6.8; N, 10.8%.

The necessary starting material was prepared as follows:-

Aluminium chloride (33.35g) was added portionwise to a stirred cooled (<0°C) solution of methyl phenoxyacetate (14.46ml) and 3-chloropropionyl chloride (9.55ml) in dichloromethane (500ml). After the addition the ice-bath was removed and the mixture stirred for 1 hour when it was poured into ice-water (500ml). The organic phase was separated and the aqueous portion extracted two times with dichloromethane. The combined dichloromethane extracts were washed with water, then brine and dried ($MgSO_4$). The residue, after removal of the solvent in vacuo and trituration with ether gave methyl 4-[3-chloropropanoyl]phenoxyacetate, 22.3g, as a solid: m.p. 89 - 90°C; NMR (d^6DMSO) δ 7.95(2H,d), 7.05(2H,d), 4.92(2H,s), 3.91(2H,t), 3.71(3H,s), 3.49(2H,t); m/e 257(M+H)$^+$; calculated for $C_{12}H_{13}ClO_4$: C, 56.1; H, 5.0. found: C, 55.8; H, 5.1%.

EXAMPLE 8: 4-[3-[4-(4-Pyridyl)piperazin-1-yl]propanoyl]phenoxyacetic acid

In a similar manner to Example 2, but starting from the product of Example 7, the title compound was prepared in 60% yield: m.p. 238 - 239°C; NMR (d^6DMSO + d^4 acetic acid) δ 8.21(2H,d), 7.97(2H,d), 7.15(2H,d), 7.02(2H,d), 4.77(2H,s), 3.64(4H,t), 3.21(2H,t), 2.82(2H,t), 2.62(4H,t); m/e 370(M+H)$^+$; calculated for $C_{20}H_{23}N_3O_4$: C, 65.0; H, 6.3; N, 11.4. found C, 64.6; H, 6.4; N, 11.1%.

EXAMPLE 9: Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenylthioacetate

In a similar manner to Example 3, but starting from methyl 4-bromoacetylphenylthioacetate, the title compound was prepared in 27% yield: m.p. 109-110°C; NMR (d^6DMSO) δ 8.15(2H,d), 7.93(2H,d), 7.40(2H,d), 6.80(2H,d), 4.07(2H,s), 3.86(2H,s), 3.66(3H,s), 3.30(4H,t), 2.61(4H,t); m/e 386 (M+H)$^+$; calculated for $C_{20}H_{23}N_3O_3S$. 0.25 H_2O: C, 61.4; H, 6.0; H, 10.7. found C, 61.8; H, 6.0; H, 10.6%.

The necessary starting material was prepared as follows:-

Aluminium chloride (18.03g) was added portionwise to a stirred cooled (<5°C) solution of methyl phenylthioacetate (9.84g) and bromoacetyl chloride (4.46ml) in dichloromethane (250ml) keeping the temperature below 5°C. The mixture was then stirred for one hour at ambient temperature then poured onto ice. After a filtration, the organic phase was separated and the aqueous portion extracted two times with dichloromethane. The combined dichloromethane extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated to give 4-bromoacetylphenylthioacetate; 11.52g, as a solid: m.p. 48 - 50°C; NMR ($CDCl_3$) δ 7.91(2H,d), 7.40(2H,d), 4.39(2H,s), 3.76(5H,s); m/e 302/304 (M+H)$^+$, 1 Br pattern.

EXAMPLE 10: 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenylthioacetic acid

In a similar manner to Example 2, but starting from the product of Example 9, the title compound was prepared in 83% yield: m.p. 240-244°C; NMR(d^6DMSO) δ 8.16(2H,d), 7.93(2H,d), 7.39(2H,d), 6.66(2H,d), 3.92(2H,s), 3.86(2H,s), 3.38(4H,t), 2.64(4H,t); m/e 372(M+H)$^+$; calculated for $C_{19}H_{21}N_3O_3S$. 0.25H_2O: C, 60.6; H, 5.7; N, 11.2. found C, 60.5; H, 5.6; N, 10.8%.

EXAMPLE 11: Methyl 3-[2-[4-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenyl]propionate

A solution of methyl 3-(4-bromoacetylphenyl)propionate (380mg) in acetonitrile (4ml) was added dropwise over 15 minutes to a stirred solution of 1-(4-pyridyl)piperazine (450mg) in acetonitrile (10ml) and the mixture stirred overnight. The mixture was then filtered and the filtrate concentrated in vacuo to give an oil. Purification by flash chromatography on silica eluting first with dichloromethane then 5% v/v methanol/dichloromethane gave a solid. Trituration with ether gave the title compound, 172mg, as a solid: m.p. 141-143°C; NMR(d^{6}DMSO) δ 8.15(2H,d), 7.92(2H,d), 7.37(2H,d), 6.83(2H,d), 3.89(2H,s), 3.59(3H,s), 3.37(4H,t), 2.93(2H,t), 2.69(2H,t), 2.65(4H,t); m/e 368(M+H)$^+$; calculated for $C_{21}H_{25}N_3O_3$. 0.25H_2O: C, 67.8; H, 6.9; N, 11.3. found: C, 67.8; H, 6.9; N,11.1%.

EXAMPLE 12: 3-[2-[4-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenyl]propionic acid

A stirred solution of the product of Example 11 (70mg) in methanol (0.5ml) was treated with a M sodium hydroxide solution (0.19ml) and stirring continued for 3 hours. The methanol was removed in vacuo and the residue diluted with water (1ml), then a M hydrochloric acid solution (0.19ml) added. On cooling to 4°C a solid precipitated which was collected, washed with ice-water, then dried to give the title compound, 36.5mg: m.p. 245-247°C; NMR (d^{6}DMSO) δ 8.05(2H,d), 7.91(2H,d), 7.36(2H,d), 6.86(2H,d), 3.89(2H,s), 3.34(4H,t), 2.87(2H,t), 2.62(4H,t), 2.58(2H,t); m/e 354 (M+H)$^+$: calculated for $C_{20}H_{23}N_3O_3$.0.2 H_2O: C, 67.2; H, 6.6; N, 11.8. found: C, 67.6; H, 6.6; N, 11.4%.

EXAMPLE 13: Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenylacetate

A solution of methyl 4-chloroacetylphenylacetate (260mg) in acetonitrile (4ml) was added dropwise over 15 minutes to a stirred solution of 1-(4-pyridyl)piperazine (375mg) in acetonitrile (10ml) and the mixture stirred overnight. The supernatent was decanted from the solid formed, concentrated in vacuo and purified by flash chromatography on neutral alumina, eluting with dichloromethane then 0.25% v/v methanol/dichloromethane and finally 0.5% v/v methanol dichloromethane. Concentration of the fractions in vacuo gave the title compound, 96mg, as a white crystalline solid: m.p. 127 - 129°C; NMR (d^{6}DMSO) δ 8.15(2H,d), 7.98(2H,d), 7.41(2H,d), 6.81(2H,d), 3.91(2H,s), 3.78(2H,s), 3.53(3H,s), 3.33(4H,t), 2.64(4H,t); m/e 354(M+H)$^+$; calculated for $C_{20}H_{23}N_3O_3$: C, 68.0; H, 6.6; N, 11.9. found: C, 68.2; H, 6.6; N, 11.9%.

EXAMPLE 14: Ethyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenylacetate

Using a method similar to that of Example 13, but starting from ethyl 4-chloroacetylphenylacetate and purification by flash chromatography on silica, eluting with dichloromethane then 5% v/v methanol/dichloromethane, the title compound was prepared in 13% yield as solid: m.p. 122 - 124°C; NMR(d^{6}DMSO) δ 8.01(2H,d), 7.29(2H,d), 7.25(2H,d), 6.67(2H,d), 3.93(2H,q), 3.75(2H,s), 3.60(2H,s), 3.18(4H,t), 2.47(4H,t), 1.03(3H,t); m/e 368 (M+H)$^+$; calculated for $C_{21}H_{25}N_3O_3$: C, 68.6; H, 6.9: N, 11.4. found: C, 68.2; H, 6.8; N, 11.3%.

EXAMPLE 15: 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenylacetic acid, trifluoroacetate salt

A stirred solution of the product of Example 13 (142mg) in methanol (1ml) was treated with M sodium hydroxide solution (0.46ml) and stirring continued for 2 hours. The methanol was removed in vacuo, the residue diluted with water (1ml), then a M hydrochloric acid solution (0.46ml) was added. This solution was transferred to a 1 inch preparative reverse phase hplc column (VYDAC^R 218TP1022) and eluted with water/acetonitrile/trifluoroacetic acid in a gradient from 98:2:0.1 v/v/v to 75:25:0.1 v/v/v. The pure fractions, on freeze-drying gave, the title compound 96mg, as a foam: NMR (d^{6}DMSO) δ 8.34(2H,d), 7.95(2H,d), 7.48(2H,d), 7.25(2H,d), 4.67(2H,b), 3.93(4H,b), 3.72(2H,s), 3.20(4H,b); m/e 340 (M+H)$^+$; calculated for $C_{19}H_{21}N_3O_3$. 2.25 CF_3COOH: C, 47.4; H, 3.9; N, 7.1. found: C, 47.8; H, 3.8; N, 7.0%.

EXAMPLE 16: RS Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]-2-methylacetyl]phenoxyacetate

A solution of RS methyl 4-(2-methylacetyl)phenoxyacetate (1.2g) in acetonitrile (10ml) was added dropwise over 30 minutes to a stirred solution of 1-(4-pyridyl)piperazine (1.3g) in acetonitrile (30ml) and the mixture stirred overnight. The mixture was then filtered and the filtrate evaporated to give an oil. Purification by flash chromatography, eluting first with dichloromethane then successively 2.5%, 3%, 4%, 5% and 10% v/v methanol/dichloromethane gave the title compound, 220mg as a solid: m.p. 81 - 83°C; NMR (d^{6}DMSO) δ 8.13(2H,d), 8.06(2H,d), 7.02(2H,d), 6.77(2H,d), 4.92(2H,s), 4.33(1H,q), 3.72(3H,s), 3.26(4H,t), 2.63(4H,t), 1.16(3H,d); m/e 384$(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4$: C, 65.8; H, 6.6; N, 11.0. found C, 65.7; H, 6.8; N, 10.9%.

EXAMPLE 17: RS 4-[2-[4-(4-pyridyl)piperazin-1-yl]-2-methylacetyl]phenoxyacetic acid sodium chloride adduct dihydrate

A stirred solution of the product of Example 16, (110mg) in methanol (1ml) was treated with a M sodium hydroxide solution (0.32ml) and stirring continued overnight. The methanol was removed in vacuo and the residue diluted with water and a M hydrochloric acid solution (0.32ml) added. The solvent was removed in vacuo to give a yellow foam which, on trituration with ether gave the title compound, 116mg: NMR (D^6DMSO) δ 8.17 (2H,d), 8.06(2H,d), 7.01(2H,d), 6.98(2H,d), 4.76(2H,s), 4.37(1H,q), 3.47(4H,t), 2.15(4H,t), 1.16(3H,d), m/e 370 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4$.NaCl. $2H_2O$: C, 51.8; H,5.8; N, 9.1. found: C,52.0; H, 5.6; N, 8.9%.

EXAMPLE 18: 2,2'-[4-(3-(4-(4-pyridyl)piperazin-1-yl]propanoyl]phenylene-1,2-dioxy]diacetate, trifluoroacetate salt

Di-tertiary butyl 2,2'-[4-[3-[4-(4-pyridyl)piperazin-1-yl-propanoyl]phenylene-1,2-dioxy]diacetate (555mg) was dissolved in 90% v/v trifluoroacetate acid/water (15ml) and the mixture stirred for one hour. The solvent was removed by evaporation in vacuo and the residual oil on trituration with ether gave the title compound, 608mg, as a solid: m.p. 42-44°C; NMR (d^6DMSO) δ 8.26(2H,d), 7.15(2H,d), 6.80(3H,m), 4.67(2H,s), 4.63(2H,s), 3.65(8H,b), 3.39(1H,q), 2.75(2H,m), 2.66(2H,m), 1.09(1.5H,t); m/e 444 $(M+H)^+$; calculated for $C_{22}H_{25}N_3O_7$. 1.3 CF_3COOH. $1H_2O$. 0.25 $C_4H_{10}O$: C, 48.9; H, 4.9; N, 6.7. found C, 49.1; H, 5.0; N, 6.3%; calculated CF_3COOH; 23.6. found 23.2%.

The necessary starting material was prepared as follows:-

(i) Solid sodium hydride (1.6g of a 60% w/w dispersion in mineral oil) was added to a stirred, cooled (4°C) solution of 3,4-dihydroxybenzaldehyde (2.76g) in THF (50ml). The mixture was then stirred for a further 15 minutes at ambient temperature, cooled to 4°C when tertiary butyl bromoacetate (6.5ml) was added followed by DMF (5ml). After one hour the mixture was diluted with ether (100ml), washed with water and brine, then dried ($MgSO_4$) and evaporated to give a solid. Recrystallisation from cyclohexane gave di-tertiary butyl 2,2'-([4-formyl])phenylene-1,2-dioxy)diacetate, 4.1g, as pale yellow crystals: m.p. 96°C; NMR (d^6DMSO) δ 9.82(1H,s), 7.54(1H,dd), 7.33(1H,d), 7.08(1H,d), 4.82(2H,s), 4.75(2H,s), 1.43(18H,s), m/e 366 (M+); calculated for $C_{19}H_{26}O_7$; C, 62.4; H, 7.3. found C, 62.3; H, 7.2%.

(ii) To a solution of the product of step (i) (10.0g) and malonic acid (42g) in pyridine (150ml) was added a few drops of piperidine and the mixture heated on a steam-bath for 4 hours. The pyridine was removed in vacuo, water 300ml added and the mixture extracted with ether (3 x 100ml). The combined extracts were washed with water, brine, dried ($MgSO_4$) then evaporated to give a gum. Recrystallisation from cyclohexane gave di-tertiary butyl 2,2'-([4-(3-propenoic acid)]phenylene-1,2-dioxy)diactate. 0.5 cyclohexane adduct, 6.6g, m.p. 104-106°C; NMR (d^6DMSO) δ 12.20(1H,b), 7.48(1H,d), 7.26(1H,s), 7.20(1H,d), 6.89(1H,d), 6.40(1H,d), 4.74(2H,s), 4.72(2H,s), 1.43(18H,s), 1.40(6H,s); m/e 408 (M+).

iii) 10% w/w palladium on charcoal (250mg) was added to a solution of the product of step (ii) (2.05g) in ethyl acetate (100ml) and the mixture hydrogenated at room temperature and pressure until the theoretical amount of hydrogen had been taken up. Charcoal was added, the mixture stirred for 5 minutes then filtered through diatomaneous earth and the filtrate evaporated to dryness giving di-tertiary butyl 2,2'-(4-[1-(2-carboxyethyl)]phenylene-1,2-dioxy)diacetate, 1.9g, as a colourless gum: NMR ($CDCl_3$) δ 6.76(3H,m), 4.58(2H,s), 4.56(2H,s), 2.86(2H,t), 2.60(2H,t), 1.47(18H,s); m/e 410(M+). This gum slowly crystallised to give a white solid of m.p. 68 - 70°C; calculated for $C_{21}H_{30}O_8$: C, 61.5; H, 7.4. found: C,61.7; H, 7.7%.

(iv) To a stirred solution of the product of step (iii) (615mg) in dry DMF was added N,N'-diiosopropylethylamine (0.78ml), HOBT (230mg), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (596mg). After 15 minutes 1-(4-pyridyl)piperazine (245mg) was added and stirring continued overnight. The DMF was removed in vacuo, the resulting oil partitioned between ethyl acetate (60ml), and water (20ml). The organic phase was separated, washed successively with water (20ml), M sodium hydroxide solution (20ml), brine (3 x 20ml) then dried and the solvent evaporated to give an oil. Purification of this oil by flash chromatography on silica, eluting with 6.5% v/v methanol in dichloromethane gave di-tertiarybutyl 2,2'--[4-[3-[4-(4-pyridyl)-piperazin-1-ylpropanoyl]phenylene-1,2-dioxy]diacetate, 728mg, as a froth: m.p. 57 - 61°C, NMR (d^6DMSO) δ 8.16(2H,d), 6.80(5H,m), 4.63(2H,s), 4.59(2H,s), 3.58(4H,b), 3.32(4H,b), 2.73(2H,m), 2.61(2H,m), 1.45(18H,s); m/e 556$(M+H)^+$; calculated for $C_{30}H_{41}N_3O_7$. $0.5H_2O$: C, 63.8; H, 7.5; N, 7.4. found: C, 63.5; H, 7.4; N, 7.1%.

EXAMPLE 19: Methyl 2-S-(n-butylsulphonylamino)-3-[4-[1- (4-pyridyl)piperidin-4-yl]methoxyphenyl]propionate

n-Butylsulphonyl chloride (0.32ml) was added dropwise to a solution of methyl 2-S-amino-3-[4-(1-(4-pyridyl)piperidin-4-yl)methoxyphenyl]-propionate (750mg) and triethylamine (0.5ml) in dichloromethane (15ml) cooled in an ice bath. The mixture was allowed to reach ambient temperature and stirred for 5 hours and then refluxed for 2 hours. The reaction mixture was washed with water (20ml) and saturated sodium chloride solution (15ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by flash chromatography eluting with methanol/dichloromethane (1:9v/v) to give the title compound (650mg) as a gum; NMR($CDCl_3$): 0.87(t,3H), 1.26-1.7(m,6H), 1.95(d,2H), 2.1(m,1H), 2.72-3.18(m,6H), 3.77(s,3H), 3.79(d,2H), 3.96(d,2H), 4.32(m,1H), 4.82(brd,1H), 6.69(d,2H), 6.83(d,2H), 7.1(d,2H), 8.25(brd,2H); mass spectrum (+ve FAB MeOH/NBA): 490 $(M+H)^+$ $[\alpha]_D^{22}$ = -14°C (c = 1, MeOH).

The starting material was prepared as follows:-

(i) Diethylazodicarboxylate (0.58ml) was added dropwise to a stirred mixture of 4-(4-hydroxymethylpiperidin-1-yl)pyridine (700mg), N-benzyloxycarbonyl-S-tyrosine methyl ester (1.2g), triphenylphosphine (955mg) and THF (40ml) in an atmosphere of argon and cooled to 10 °C. The mixture was allowed to reach ambient temperature and stirred for 48 hours. The solvent was removed by evaporation and the residue purified by flash chromatography eluting with methanol/dichloromethane (1:9v/v) to give methyl 2S-(benzyloxycarbonylamino)-3-[4-(1-(4-pyridyl)piperidin-4-yl)methoxyphenyl]propionate (1.2g) as a solid m.p. 68-75 °C; NMR(d_6-DMSO): 1.2-1.4(m,2H), 1.84(d,d,2H), 1.92-2.1(m,1H), 2.7-3.02(m,4H), 3.6(s,3H), 3.8(d,2H), 3.98(d,2H), 4.14-4.28(m,1H), 4.98(s,2H), 6.78-6.88(m,4H), 7.13(d,2H), 7.20-7.4(m,5H), 7.75(d,1H), 8.13(d,2H); mass spectrum (+ve FAB, MeOH/NBA): 504$(M+H)^+$.

(ii) A solution of the product of step (i) (1g) in ethanol (40ml) and 10% palladium/carbon (200mg) was stirred in a stream of hydrogen for 4 hours at ambient temperature. The mixture was filtered through a pad of diatomaceous earth and the solvent removed by evaporation to give methyl 2-S-amino-3-[4-(1-(4'-pyridyl)piperidin-4-yl)methoxyphenyl]propionate as an oil; NMR(d_6DMSO): 1.13-1.44(m,2H), 1.75-2.13(m,3H), 2.64-2.94(m,4H), 3.51(m,1H), 3.57(s,3H), 3.81(d,2H), 3.96(d,2H), 6.8(dd,2H), 6.83(d,2H), 7.08(d,2H), 8.12(dd,2H); mass spectrum(+ve FAB, MeOH/NBA): 370 $(M+H)^+$.

EXAMPLE 20: 2-S-(n-butylsulphonylamino)-3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]propionic acid

Lithium hydroxide (285mg) was added to a solution of the product of Example 33 (520mg) in a mixture of methanol (9ml), THF (9ml) and water (9ml) and stirred at ambient temperature for 3.75 hours. The solvent was evaporated and water (5ml) added to the residue. A 10% aqueous solution of potassium hydrogen sulphate (8ml) was added and an oil separated. The oil was dissolved in methanol and filtered through diatomaceous earth. The solvent was evaporated, and the residue triturated with ethyl acetate gave the title compound (500mg) as an amorphous solid, NMR (d_6DMSO)): 0.81(t,3H), 1.1-1.6(m,6H), 1.85(d,2H), 2.0(brs,1H), 2.58-3.0(m,6H), 3.68(t,2H), 3.8(d,2H), 3.98(d,2H), 6.8(brs,4H), 7.13(d,2H), 8.12(brs,2H); mass spectrum(+ve FAB, methanol/m-nitrobenzyl alcohol(NBA)): 476$(M+H)^+$.

EXAMPLE 21: Methyl 2-S-(n-butylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionate

n-Butylsulphonyl chloride (0.28ml) was added dropwise to a solution of methyl 2-S-amino-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionate (630mg) and triethylamine (0.5ml) in dichloromethane (15ml) cooled in an ice-bath. The mixture was allowed to reach ambient temperature and stirred for 5 hours. The reaction mixture was diluted with dichloromethane (10ml) and washed with water (20ml), saturated sodium chloride solution (10ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by flash chromatography eluting with methanol/dichloromethane(1:9v/v) to give the title compound (680mg) as a gum; NMR($CDCl_3$): 0.9(t,3H), 1.25-1.45(m,4H), 1.55-1.95(m,7H), 2.72-3.15(m,6H), 3.78(s,3H), 3.9(brd,2H), 4.0(t,2H), 4.32(brs,1H), 4.84(brs,1H), 6.68(d,2H), 6.83(d,2H), 7.09(d,2H), 8.23(brs,2H); mass spectrum(+ve FAB, MeOH/NBA): 504 $(M+H)^+$.

The starting material was prepared as follows:-

(i) Following the method of Example 19, step (i), but using 4-(4-hydroxyethylpiperidin-1-yl)pyridine, methyl 2-S-(benzyloxycarbonylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionate (900mg) was prepared as an oil; NMR (d_6DMSO): 1.05-1.35(m,2H), 1.6-1.9(m,5H), 2.7-3.05(m,4H), 3.63(s,3H), 3.92(d,2H), 4.0(t,2H), 4.21(m,1H), 4.98(s,2H), 6.8(d,2H), 6.84(d,2H), 7.14(d,2H), 7.3(m,4H), 7.75(d,1H), 8.12(d,2H); mass spectrum(+ve

FAB, NBA/CH_2Cl_2): 518 $(M+H)^+$.

(ii) Following the method of Example 19, step (ii), but using the product of step (i) above, methyl 2-S-amino-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionate was prepared as a gum; NMR(d_6DMSO): 1.08-1.32(m,2H), 1.58-1.86(m,5H), 2.61-2.9(m,4H), 3.52(m,1H), 3.58(s,3H), 3.82-4.02(m,4H), 6.79(dd,2H), 6.81(d,2H), 7.07(d,2H), 8.1(dd,2H); mass spectrum(+ve FAB, MeOH/NBA): 384 $(M+H)^+$.

EXAMPLE 22: 2-S-(n-butylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionic acid

Following the method of Example 20, but using the product of Example 21 the title compound (380mg) was prepared; NMR(d_6DMSO): 0.78(t,3H), 1.05-1.5(m,6H), 1.6-1.9(m,5H), 2.5-3.05(m,6H), 3.8-4.05(m,6H), 4.6(brs,1H), 6.85(m,4H), 7.19(d,2H), 8.13(brs,2H); mass spectrum(+ve FAB, MeOH/NBA): 490 $(M+H)^+$; microanalysis found: C, 57.7; H, 7.5; N, 8.0; H_2O, 7.1%; $C_{25}H_{35}N_3O_5S.2H_2O$ requires: C, 57.1; H, 7.4; N, 8.0; H_2O, 6.9%.

EXAMPLE 23: Methyl 2-S-(n-butylsulphonylamino)-3-[4-[1-(4-pyridyl)piperidin-4-yl]oxyphenyl] propionate

Using a procedure similar to that described in Example 21, but starting from the appropriate amino acid ester, the title compound was prepared NMR($CDCl_3$): 0.9(t,3H), 1.25-1.45(m,2H), 1.55-1.8(m,2H), 1.8-2.15(m,4H), 2.6-2.88(m,2H), 2.9-3.2(m,2H), 3.3-3.45(m,2H), 3.55-3.74(m,2H), 3.78(s,3H), 4.27-4.4(m,1H), 4.45-4.6(m,1H), 4.8(brd,2H), 6.7(d,2H), 6.86(d,2H), 7.1(d,2H), 8.26(brd,2H); mass spectrum (+ve FAB, MeOH/NBA): 476 $(M+H)^+$.

The starting material was prepared using similar procedures to those described in Example 21. There were thus prepared the following intermediates starting from 4-(4-hydroxypiperidin-1-yl)pyridine:-

Methyl 2-S-(benzyloxycarbonylamino)-3-[4-(1-(4'-pyridyl)piperidin-4-yl)oxyphenyl]propionate; NMR(d_6DMSO): 1.5-1.72(m,2H), 1.9-2.1(m,2H), 2.7-3.02(m,2H), 3.18(d,2H), 3.2-3.35(m,1H), 3.48-3.77(m,1H), 3.62(s,3H), 4.13-4.28(m,1H), 4.5-4.65(m,1H), 4.97(s,2H), 6.8-6.94(m,4H), 7.14(d,2H), 7.77(d,1H), 8.15(d,2H); mass spectrum(+ve FAB, CH_2Cl_2/NBA): 518 $(M+H)^+$.

Methyl 2-S-amino-3-[4-(1-(4'-pyridyl)piperidin-4-yl)oxyphenyl]propionate; NMR(d_6DMSO): 1.54-1.72(m,2H), 1.9-2.06(m,2H), 2.65-2.88(m,2H), 3.15-3.4(m,2H), 3.52(t,1H), 3.59(s,3H), 3.6-3.75(m,2H), 4.52-4.65(m,1H), 6.8-6.92(m,4H), 7.09(d,2H), 8.15(dd,2H); mass spectrum (+ve FAB, MeOH/NBA): 356 $(M+H)^+$.

EXAMPLE 24: 2-S-(n-butylsulphonylamino)-3-[4-[1-(4-pyridyl)piperidin-4-yl]oxyphenyl]propionic acid

Using a similar procedure to that described in Example 20 but starting from the product of Example 23, the title compound was obtained as a solid m.p.255-258°C dec.; NMR(d_6DMSO): 0.66 (t,3H), 0.98-1.04 (m,2H), 1.05-1.4(m,2H), 1.44-1.62(m,2H), 1.8-1.96(m,2H), 2.49(t,2H), 2.61(dd,1H), 2.87(dd,1H), 3.12-3.28(m,2H), 3.4-4.0(m,5H), 4.43-4.55(m,1H), 6.79(m,4H), 7.09(d,2H), 8.04(brd,2H); mass spectrum(+ve FAB, MeOH/NBA): 462 $(M+H)^+$; microanalysis found: C, 59.6; H 6.9; N, 9.0%; $C_{23}H_{31}N_3O_5S$ requires: C, 59.8; H, 6.8; N, 9.1%.

EXAMPLE 25: Ethyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyrate

A stirred suspension of 4-((4-pyridyl)piperazin-1-yl)phenol (1.34g) in dry DMF (20ml) was treated with sodium hydride (60% dispersion in mineral oil, 0.21g) and the mixture stirred for 1 hour. To the resulting solution was added ethyl 4-bromobutyrate and the mixture was stirred for 16 hours. Solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water, filtered through phase separating paper (Whatman 1PS) and evaporated. The residue was purified by flash chromatography on silica, eluting with 1.5/92.5/6 v/v/v methanol/ethyl acetate/aqueous ammonia (SG 0.89) and recrystallised from ethyl acetate/hexane to give the title compound (0.7g) as a solid: m.p. 84-85°C; NMR ($CDCl_3$) δ 8.3(2H,d); 6.86(4H,c); 6.72(2H,d); 4.12(2H,q); 4.0(2H,t); 3.47(4H,m); 3.20(4H,m); 2.5(2H,t); 2.1(2H,m); 1.26(3H,t); m/e 370$(M+H)^+$; calculated for $C_{21}H_{27}N_3O_3$ C, 68.3; H, 7.4; N, 11.4. Found: C, 68.1; H, 7.4; N, 11.1%.

The necessary starting material was prepared as follows:-

(i) 4-(piperazin-1-yl)anisole (4.24g) and 4-chloropyridine hydrochloride (3.35g) were intimately mixed and heated at 160-170°C (bath temperature) for 7 minutes. The solid obtained on cooling was dissolved in water (75ml) and the solution basified with aqueous ammonia. The solid precipitate was extracted into ethyl acetate and the organic extract washed with water, filtered through phase separating paper (Whatman 1PS) and evaporated. The residue was recrystallised from ethanol to give 4-[(4-pyridyl)piperazin-1-yl]anisole (1.84g) as a solid: m.p. 165-167°C; NMR ($CDCl_3$) δ 8.3(2H,d); 6.86(4H,m); 6.71(2H,d); 3.78(3H,s); 3.46(4H,m); 3.2(4H,m).

(ii) The product from step (i) (1.5g) in concentrated hydrobromic acid (30ml) was heated under argon at 130-135°C for 2 1/2 hours. The solution was cooled, poured into water (150ml) and basified with aqueous ammonia. The precipitate was filtered, washed with water and dried to give 4-[(4-pyridyl)piperazin-1-yl]phenol (1.36g) as a solid: m.p. 310-312°C; NMR(d_6DMSO) δ 8.2(2H,d); 6.8(4H,m); 6.66(2H,d); 3.45(4H,m); 3.08(4H,m).

EXAMPLE 26: 4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyric acid

A solution of the product of Example 25 (0.1g) in aqueous sodium hydroxide (1N, 0.8ml) and ethanol (2ml) was kept for 2 hours. The solution was evaporated and the residue dissolved in water (5ml). Hydrochloric acid (1N, 0.8ml) was added and the precipitate was filtered and washed with water and ether to give the title compound as a solid: m.p. 305-306°C; m/e 342(M+H)$^+$; NMR(d_6DMSO) δ 8.0(2H,d); 6.72(6H,m); 3.74(2H,t); 3.3(4H,m); 2.94(4H,m); 2.19(2H,t); 1.72(2H,m); calculated for $C_{19}H_{23}N_3O_3$: C, 66.8; H, 6.8; N, 12.3. Found: C, 67.0; H, 6.8; N, 12.2%.

EXAMPLE 27: Ethyl 5-[4-(4-pyridyl)piperazin-1-yl]phenoxypentanoate

In a similar manner to Example 25, but starting from ethyl 5-bromopentanoate, was prepared the title compound in 41% yield (from ethyl acetate/hexane): m.p. 79-82°C; NMR($CDCl_3$) δ 8.2(2H,d), 6.88(4H,m), 6.7(2H,d), 4.13(2H,q), 3.47(4H,m), 3.17(4H,m), 2.36(2H,m), 1.8(4H,m), 1.33(3H,t); m/e 384(M+H)$^+$; calculated for $C_{22}H_{29}N_3O_3$. 0.25H_2O: C, 68.1; H, 7.6; N, 10.8. Found: C, 68.2; H, 7.8; N, 10.5%.

EXAMPLE 28: 5-[4-(4-pyridyl)piperazin-1-yl]phenoxypentanoic acid

In a similar manner to Example 26, but starting from the product of Example 27, the title compound was made in 50% yield: m.p. 237-241°C; NMR(d_6DMSO) δ 8.2(2H,d); 6.97(4H,m), 6.83(2H,d); 3.69(2H,t), 3.57(4H,m), 3.13(4H,m); 2.27(2H,t), 1.67(4H,m); m/e 356(M+H)$^+$; calculated for $C_{20}H_{25}N_3O_3$ 0.75H_2O: C, 65.0; H, 7.2; N, 11.3. Found: C, 65.0; H, 6.9; N, 11.1%.

EXAMPLE 29: Ethyl 4-[4-(4-pyridyl)piperazin-1-yl]phenoxycrotonate

In a similar manner to Example 25, but starting from ethyl 4-bromocrotonate, was prepared the title compound in 3% yield (from ethyl acetate/hexane): m.p. 127-128°C; NMR($CDCl_3$) δ 8.3(2H,d), 7.1(1H,m), 6.9(4H,m), 6.7(2H,m), 6.18(2H,m), 4.66(2H,m), 4.25(2H,q), 3.49(4H,m), 3.2(4H,m), 1.3(3H,t); m/e 368(M+H)$^+$; calculated for $C_{21}H_{25}N_3O_3$: C, 68.6; H, 6.9; N, 11.4. Found C, 68.4; H, 6.9; N, 10.7%.

EXAMPLE 30: Methyl 3-[4-[4-(4-pyridyl)piperazin-1-yl]]benzanidopropionate

Methyl 3-aminopropionate hydrochloride (0.195g) and triethylamine (0.59ml) were added to a stirred suspension of 4-[(4-pyridyl)piperazin-1-yl]benzoyl chloride hydrochloride (0.473g) at room temperature. The mixture was stirred for two days and solvent removed under reduced pressure. The residue was purified by flash column chromatography. The product was obtained by elution with 1/9/0.1 v:v:v methanol/dichloromethane/0.88 S.G. aqueous ammonia as a solid which was recrystallised from ethyl acetate to give the title compound (0.2g): m.p. 197-199°C; NMR(d_6DMSO) δ 8.19(2H,d); 7.72(2H,d); 7.13(2H,d); 6.90(2H,d); 3.82(4H,m); 3.56(3H,s); 3.48(6H,m), 2.50(2H,t); m/e 369(M+H)$^+$; calculated for $C_{20}H_{24}N_4O_3$. 0.25H_2O: C,64.4; H, 6.6; N, 15.0. Found: C,64.3; H, 6.6; N, 14.9%.

The necessary starting material was obtained as follows:-

(i) An intimate mixture of 1-(4-pyridyl)piperazine (1.63g) and 4-bromobenzoic acid (1.05g) was heated at 220°C for 6 hours. The resulting glass was cooled and triturated with methanol (50ml) to give, as an off-white solid, 4-((4-pyridyl)piperazin-1-yl)benzoic acid; m.p>350°C; IR(cm^{-1}) 1682, 1600, 1514, 1236, 1013.

(ii) Oxalyl chloride (0.5ml) was added to a stirred suspension of 4-((4-pyridyl)piperazin-1-yl)benzoic acid in dichloromethane (15ml), followed by DMF (1 drop). The mixture was stirred for 2 hours and evaporated to dryness to give 4-[(4-pyridyl)piperazin-1-yl]benzoyl chloride which was used immediately.

EXAMPLE 31: 3-[4-[4-(4-pyridyl)piperazin-1-yl]]benzamidopropionic acid

To a solution of the product of Example 30 (0.062g) in methanol (1ml) was added sodium hydroxide solution (1N, 0.17ml) and the solution kept for 4 days at room temperature. Hydrochloric acid (1N, 0.17ml) was added to give the title compound as a solid (0.052g); m.p. >330°C; NMR(d_6DMSO 6.96(2H,d); 3.76(4H,m); 3.46(6H, complex); 2.5(2H,m); m/e 355 (M+H)$^+$; calculated for $C_{19}H_{22}N_4O_3$. 0.7 H_2O: C, 62.2; H, 6.4; N, 15.3. Found: C, 62.3; H, 6.4; N, 15.3%.

EXAMPLE 32: Methyl 3-[4-[4-(4-pyridyl)piperazin-1-yl]benzamido]-3-phenylpropionate

In a similar manner to Example 30, but starting from methyl 3-amino-3-phenylpropionate, was prepared the title compound in 26% yield as a solid (after trituration with hot ethyl acetate); NMR(d_6DMSO) δ 8.6(1H,d); 8.2(1H,broad s); 7.75(2H,d); 7.3(5H,m); 7.0(2H,d); 6.85(2H, broad s); 5.45(1H,m); 3.55(3H,s); 3.45(8H,m); 292(2H,m); m/e 445$(M+H)^+$; calculated for $C_{26}H_{28}N_4O_3$. $0.5H_2O$: C, 68.9; H, 6.4; N, 12.4. Found. C, 68.7; H, 6.3; N, 12.3%.

EXAMPLE 33: 3-[4-[4-(4-pyridyl)piperazin-1-yl]benzamido]-3-phenylpropionic acid

In a similar manner to Example 26, but starting from the product of Example 32, was prepared the title compound in 73% yield as a solid; NMR(d_6DMSO) δ 8.61(1H,d); 8.2(2H,broad s); 7.78(2H,d); 7.3(5H,m); 7.0(2H,d); 6.9(2H,d); 5.43(1H,m); 3.45(8H,m); 2.82(1H,m); m/e 431(M+H)+; calculated for $C_{25}H_{26}N_4O_3$ $0.5H_2O$: C, 68.3; H, 5.9; N, 12.8. Found: C, 68.3; H, 6.0; N, 12.9%.

EXAMPLE 34: Methyl 3-[4-[4-(4-pyridyl)piperazin-1-yl]benzamido]butyrate

In a similar manner to Example 30, but starting from methyl 3-aminobutyrate, was prepared the title compound in 11% yield (recrystallised from ethyl acetate/hexane) as a solid; m.p. 130-132°C. NMR (d_6DMSO) δ 8.28(2H,d); 8.07(1H,d); 7.77(2H,d); 7.13(2H,d); 7.0(2H,d); 4.36(1H,m); 3.74(4H,m); 3.6(3H,s); 3.48(4H,m); 2.55(2H,m); 1.2(3H,d); m/e 383$(M+H)^+$; calculated for $C_{21}H_{26}N_4O_3$. $0.25H_2O$: C, 65.2; H, 6.9; N, 14.5. Found: C, 65.3; H, 6.8; N, 14.4%.

EXAMPLE 35: Methyl 4-[2-[4-(4-pyridyl)piperazin-2-one-1-yl]acetyl]phenoxyacetate

A dispersion of potassium hydride in mineral oil (35% w/w, 0.63g) was added to a stirred suspension of 4-(4-pyridyl)piperazin-2-one (0.885g) in DMF (10ml) and the mixture was stirred at room temperature for 2 hours.

To the anion thus formed, was added methyl 4-bromoacetylphenoxyacetate (1.44g) and the mixture was stirred at room temperature for 20 hours. Solvent was evaporated and the residue partitioned between dichloromethane (20ml) and water (20ml). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography, the product being eluted with 1/9/0.1 v:v:v methanol/dichloromethane/0.88 S.G aqueous ammonia. Recrystallisation from ethyl acetate gave the title compound, m.p. 164-165°C; NMR(d_6DMSO) δ 8.2(2H,d), 7.97(2H,d), 7.08(2H,d), 6.83(2H,d), 4.93(4H,d), 4.02(2H,s), 3.71(3H,s), 3.7(2H,m), 3.52(2H,m); m/e 384 $(M+H)^+$; calculated for $C_{20}H_{21}N_3O_5$: C, 62.7; H, 5.52; N, 11.0. Found: C, 62.6; H, 5.6; N, 10.9%.

The necessary starting material was prepared as follows:-

An intimate mixture of piperazinone (4.2g) and 4-chloropyridine hydrochloride (7.33g) was stirred and heated at 200°C for 10 minutes and allowed to cool. The product was purified by flash column chromatography and eluted with 1/9/0.1 v:v:v methanol/methylene chloride/0.88 S.G. aqueous ammonia.

The solid thus obtained was recrystallised from ethanol to give 4-(4-pyridyl)piperazin-2-one (1.75g); m.p. 268-270°C; NMR(D_6DMSO) δ 8.2(3H,m); 6.8(12H,m); 3.85(2H,s); 3.52(2H,m); 3.31(2H,m); m/e 178$(M+H)^+$.

EXAMPLE 36: 4-[2-[4-(4-pyridyl)piperazin-2-one-1-yl]acetyl]phenoxyacetic acid.

In a similar manner to Example 26, but starting from the product of Example 35, was prepared the title compound in 20% yield as a solid NMR(d_6DMSO) δ 8.22(2H,d), 7.97(2H,d), 7.04(2H,d), 6.89(2H,d); 4.93(2H,s), 4.77(2H,s), 4.07(2H,s), 3.72(2H,m), 3.49(2H,m); m/e 370$(M+H)^+$); calculated for $C_{19}H_{19}N_3O_5$. $2.5H_2O$: C, 55.1; H, 5.8; N, 10.1. Found: C, 55.1; H, 5.3; N, 10.6%.

EXAMPLE 37: Methyl 4-[[4-(4-pyridyl)piperazin-1-yl]carboxamido]phenoxy acetate

To a solution of 1-(4-pyridyl)piperazine (0.4g) in dichloromethane (10ml) was added a solution of methyl 4-isocyanatophenoxyacetate (0.5g) in dichloromethane (5ml). The resulting solution was stirred for 3 hours at room temperature. Solvent was evaporated and the residue triturated with ethanol to give the title compound as a solid (0.155g); NMR(d_6DMSO) δ 8.55(1H,s), 8.22(2H,d), 7.28(2H,d), 7.02(2H,d), 6.82(2H,d), 4.72(2H,s), 3.7(3H,s), 3.58(8H,m); m/e 371$(M+H)^+$; calculated for $C_{19}H_{22}N_4O_4$. H_2O: C, 58.8; H, 6.2; N, 14.4 Found: C, 58.7; H, 5.8; N, 14.8%.

The necessary starting material was prepared as follows:-

Methyl 4-aminophenoxyacetate (2.2g) in ethyl acetate (dried with calcium chloride) (50ml) was added dropwise to a stirred solution of phosgene in toluene (115ml, ~2M) at 75°C. After addition the mixture was stirred at 75°C for 1.5 hours and at 95-105°C for 16 hours. Solvent was evaporated to give an oil (2.5g); 1R shows a strong band at $2273cm^{-1}$.

EXAMPLE 38: 4-[[4-(4-pyridyl)piperazin-1-yl]carboxamido]phenoxyacetic acid

In a similar manner to Example 26, but starting from the product of Example 37, was prepared the title compound in 86% yield as a solid; NMR(d_6DMSO) δ 8.45(1H,s); 8.2(2H,d), 7.35(2H,d), 6.35(4H,m), 4.55(2H,s), 3.49(8H,m), m/e 357(M+H)$^+$; calculated for $C_{18}H_{20}N_4O_4$. 0.75 H_2O: C, 58.5; H, 5.8; N, 15.2. Found: C, 58.5; H, 5.9; N, 15.1%.

EXAMPLE 39: Methyl 2-RS-(n-butylsulphonylamino)-3-[4-[2-[4-(4-pyridyl)-piperazin-1-yl]acetyl]phenyl]propionate

To a solution of 1-(4-pyridyl) piperazine (296mg) and triethylamine (0.25ml) in acetonitrile (10ml) was added, dropwise, over 30 minutes a solution of methyl-2-RS-(n-butylsulphonylamino)-3-(4-bromoacetylphenyl) propionate (382mg) in acetonitrile (8ml). The mixture was stirred for an additional 4 hours. The solvent was removed by evaporation to give an oil which was purified by flash column chromatography on silica, eluting with methanol/dichloromethane (5:95 to 10:90 v/v) to give the title compound as a solid (202mg): NMR(d_6DMSO) 0.7(t,3H), 1.05-1.4(m,4H), 2.55-2.7(m,4H), 2.8-3.2(m,4H), 3.25-3.4(m,4H), 3.65(s,3H), 3.9(s,2H), 4.1-4.25(m,1H), 6.85(d,2H), 7.45(d,2H), 7.95(d,1H), 7.95(d,2H), 8.15(d,2H); m/e 503(M+H)$^+$; calculated for $C_{25}H_{34}N_4O_5S.0.5H_2O$: C, 58.7; H, 6.85; N, 10.9. Found: C, 58.8; H, 6.9; N, 10.6.

The necessary starting material was prepared as follows:-

(i) Methyl 2-amino-3-(4-acetylphenyl)propionate was prepared by the method described by M.P.Doyle JOC (1977), 42, 2431 and G,H.Cleland JOC (1969), 34, 744.

(ii) n-Butylsulphonyl chloride(0.6ml) was added dropwise over 15 minutes to a solution of the product of step (i) (926mg) and triethylamine (0.7ml) in dichloromethane (20ml). The resulting mixture was stirred for a further 3 hours before it was poured into water (10ml) and extracted with dichloromethane (3 x 20ml). The organic extracts were combined, dried ($MgSO_4$) and then evaporated to give a gum. Purification by flash column chromatography on silica, eluting with ethyl acetate/hexane (40:60 v/v) gave methyl 2-RS-(n-butylsulphonylamino)-3-(4-acetylphenyl)propionate (794mg) as a solid: NMR (d_6DMSO) δ 0.75(t,3H), 1.0-1.4(m,4H), 2.55(s,3H), 2.65(s,3H), 2.8-2.95(m,2H), 3.05-3.2(m,2H), 3.65(s,3H), 4.1-4.25(m,1H), 7.45(d,2H), 7.85(d,1H), 7.9(d,2H); m/e 342(M+H)$^+$.

(iii) To a suspension of $CuBr_2$ (822mg) in ethyl acetate (8ml) at reflux was added, dropwise over 10 minutes, a solution of the product from step (ii) in chloroform (8ml). The resulting mixture was refluxed for 3 hours. The mixture was cooled, filtered and the solvent was removed by evaporation to give an oil. Purification by flash column chromatography on silica, eluting with ethyl acetate/hexane (10:90 to 50:50 in 10% increments v/v) gave methyl 2-RS-(n-butylsulphonylamino)-3-(4-bromoacetylphenyl) propionate (387mg) as an oil: NMR ($CDCl_3$) δ 0.9(t,3H), 1.25-1.4(m,2H), 1.6-1.75(m,2H), 2.75-2.85(m,2H), 3.05-3.3(m,2H), 3.8(s,3H), 4.35-4.45(m,1H), 4.4(s,2H), 4.8(d,1H), 7.35(d,2H), 7.95(d,2H); m/e 420/422 (M+H)$^+$, Br pattern.

EXAMPLE 40: 2-RS-(n-butylsulphonylamino)-3-[4-[2-[4-(4-pyridyl)piperazine-1-yl]acetyl]phenyl]propionic acid

To a solution of the product of Example 39 (105mg) in methanol (4ml) was added 2N sodium hydroxide (0.25ml) and the resulting solution was stirred for 3 hour. The mixture was concentrated, dissolved in water (2ml) and acidified with acetic acid. The resulting solution was transferred to a reverse phase hplc column (Dynamax C18 83-201-C 60A) and eluted with 0.1% TFA in water/acetonitrile. The pure fractions, on freeze drying, gave the title compound (89mg) as a solid: NMR (d_6DMSO) δ 0.8(t,3H), 1.15-1.6(m,4H), 2.75(t,2H), 2.9-3.05(m,1H), 3.2-3.3(m,1H), 3.4-3.5(m,4H), 3.95-4.2(m,5H), 4.95(s,2H), 7.25(d,2H), 7.55(d,2H), 8.0(d,2H), 8.35(d,2H); m/e 489(M+H)$^+$; calculated for $C_{24}H_{32}N_4O_5S$.3 CF_3COOH: C, 43.4 ; H, 4.2 ; N, 6.7 ; TFA, 41.2. Found C, 43.7 ; H, 4.3; N, 6.8; TFA, 42.7.

EXAMPLE 41: 2-RS-(n-Butylsulphonylamino)-3-[4-(4-pyridyl)piperazin-1-yl methylene]phenylpropionic acid

To a solution of ethyl 2-RS-(n-butylsulphonylamino)-3-[4-(4-pyridyl)piperazin-1-yl methylene]phenylpropionate in methanol (3ml) was added 2N sodium hydroxide (0.3ml). The mixture was stirred for 3 hours and then concentrated. The resulting slurry was dissolved in water (2ml) and acidified with acetic acid. The resulting solution was transfered to a reverse phase hplc column (Dynamax C18 83-201-C 60 A) and eluted with 0.1% TFA in water/acetonitrile. The pure product fractions, on freeze drying, gave the title compound (165mg) as a solid: NMR (d_6DMSO) δ 0.8(t,3H), 1.1-1.6(m,4H), 2.65-2.95(m,4H), 3.2-3.3(m,4H), 3.85-4.0(m,4H), 4.05-4.15(m,1H), 4.3(s,2H), 7.2(d,2H), 7.4(s,5H), 8.3(d,2H); m/e 461(M+H)$^+$; calculated for $C_{23}H_{32}N_4O_4S.H_2O$. 2CF_3COOH: C, 45.9 ; H, 5.1 ; N, 7.9. Found C, 45.5 ; H, 4.8 ; N, 7.5.

The starting material was prepared as follows:-

(i) To a solution of α,α'-dibromo-p-xylene (6.59g),N-(diphenylmethylene) glycine ethyl ester (4.76g) and potassium iodide in 1,4-dioxane (120ml), cooled to 10°C, was added 40% aq. benzyltrimethylammonium hydroxide(7.45ml) over 1 hour. The mixture was allowed to warm to room temperature and then to stir for 2.5 hours. The mixture was partitioned between water (50ml) and ethyl acetate (100ml). The organic layer was separated, dried ($MgSO_4$) and evaporated to give an oil. Purification by flash column chromatography on silica, eluting with ether/hexane (10:90 v/v) gave ethyl RS-N-(diphenylmethylene)-4-(bromomethyl)phenylalanine ethyl ester (3.58g) as an oil: NMR (d_6DMSO) δ 1.5(t,3H), 3.0-3.2(m,2H), 4.05-4.15(m,3H), 4.65(s,2H), 6.55-6.65(m,2H), 7.0(d,2H),7.25(d,2H), 7.3-7.5(m,8H); m/e 450/452$(M+H)^+$ Br pattern.

(ii) To a warm solution of 1-(4-pyridyl)piperazine (296mg) and triethylamine (0.14ml) in acetonitrile (15ml) was added slowly over 40 minutes a solution of the product from step (i) (409mg) in acetonitrile (5ml). The resulting mixture was stirred at room temperature for 18 hours. The mixture was concentrated and purified by flash column chromatography on silica, eluting with methanol/dichloromethane (3:97 to 10:90 v/v) to give RS-N-(diphenylmethylene)-4-[4-(4-pyridyl)piperazin-1-ylmethylene]phenylalanine ethyl ester (305mg) as a solid: NMR (d_6DMSO) δ 1.15(t,3H), 2.4-2.5(m,4H), 3.0-3.2(m,2H), 3.25-3.35(m,4H), 3.45(s,2H), 4.05-4.15(m,3H), 6.65(d,2H), 6.75(d,2H), 7.0(d,2H), 7.15(d,2H), 7.35-7.5(m,8H), 8.1(d,2H); m/e 533$(M+H)^+$.

(iii) To a suspension of the product from step (iii) in ether (5ml) was added 1N hydrochloric acid (2.2ml) and the resulting mixture was stirred for 1 hour. The mixture was partitioned between ether (20ml) and 1N hydrochloric acid(10ml). The acid layer was separated, basified with aqueous sodium bicarbonate and extracted with dichloromethane (3x 20ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated to give RS-4-[4-(4-pyridyl)-piperazin-1-ylmethylene]phenylalanine ethyl ester as an oil: NMR (d_6DMSO) δ 1.1 (t,3H), 2.4-2.5(m,4H), 2.7-2.9(m,2H), 3.2-3.35(m,4H), 3.5(s,2H), 3.5-3.6(m,1H), 4.0(q,2H), 6.8(m,2H), 7.2(dd,4H), 8.1(bm,2H); m/e 369$(M+H)^+$.

(iv) To a solution of the product of step (iii) (137mg) and triethylamine (0.11ml) in tetrahydrofuran (5ml) was added 0.75ml of a stock solution of n-butylsulphonyl chloride (0.2ml in 3ml of tetrahydrofuran) and the resulting mixture was stirred for 3 hours. The solvent was removed by evaporation to give a gum. Purification by flash column chromatography on silica, eluting with methanol/dichloromethane (5:95 to 10:90 v/v) gave ethyl 2-(RS)-(n-butylsulphonylamino)-3-[4-(4-pyridyl)piperazin-1-yl-methylene]phenylpropionate as a solid which was used without further purification.

EXAMPLE 42: 4-[[4-(4-pyridyl)piperazin-1-yl]methylene]cinnamic acid

^{t}Butyl 4-[[4-(4-pyridyl)piperazin-1-yl]methylene] cinnamate (200mg) was stirred in trifluoroacetic acid (5ml) for 2 hours. The solvent was removed by evaporation and the resulting oil was titriated with anhydrous ether to give the title compound (210mg) as a white solid: NMR (d_6DMSO) δ 3.05-3.25(m,4H), 3.7-4.1(bm,4H), 4.25(s,2H), 6.6(d,1H), 7.25(d,2H), 7.5(d,2H), 7.6(d,1H), 7.75(d,2H), 8.35(d,2H); m/e 324$(M+H)^+$; calculated for $C_{19}H_{21}N_3O_2.2CF_3COOH.0.5H_2O$: C, 49.5; H, 4.25; N, 7.4. Found: C, 49.1; H, 4.2; N, 7.1.
The necessary starting material was prepared as follows:-

(i) In a similar to Example 39, but starting from ^{t}butyl 4-bromomethyl cinnamate was prepared ^{t}butyl 4-[[4-(4-pyridyl)piperazin-1-yl]methylene] cinnamate: NMR (d_6DMSO) δ 1.45(s,9H), 3.55(s,2H), 6.5(d,1H), 6.8(d,2H), 7.35(d,2H), 7.55(d,1H), 7.65(d,2H), 8.15(d,2H).

EXAMPLE 43: Dimethyl 4-[2-[(4-(4-pyridyl)piperazin-1-yl)-2-methyl]acetyl]-1,2-diphenoxydiacetate

In a similar manner to Example 39, but starting from dimethyl 4-[(2'-bromopropionyl)-phenylene-1,2-dioxy]diacetate was prepared the title compound: NMR (d_6DMSO) δ 1.15(d,3H), 2.55-2.7(m,4H), 3.2-3.35(m,4H), 3.68(s,3H),3.70(s,3H), 4.25(q,1H), 4.9(s,2H), 4.95(s,2H), 6.75(d,2H), 7.0(d,1H), 7.65(d,1H), 7.75(dd,1H), 8.15(d,2H); m/e 472$(M+H)^+$.
The starting material was prepared as follows:-

(i) To a solution of 3,4 dihydroxypropiophenone (1.24g) in DMF (15ml) was added anhydrous potassium carbonate (3.09g) followed by methyl bromoacetate (1.4ml). The resulting mixture was stirred for 24 hours. Water (50ml) was added and the mixture was extracted with ethyl acetate (3x100ml). The organic extracts were combined, dried

($MgSO_4$) and evaporated to give a gum. Purification by flash column chromatography on silica, eluting with ethyl acetate/hexane (1:1 v/v) gave dimethyl 4-propionyl-phenylene-1,2-dioxydiacetate (1.79g) as an oil: NMR (d_6DMSO) δ 1.05(t,3H), 3.0(q,2H), 3.7(s,6H), 4.9(s,2H),4.95(s,2H), 7.05(d,d,1H), 7.45(d,1H), 7.6(dd,1H),; m/e 311(M+H)$^+$.

(ii) To a solution of the product from step (i) (1.79g) in chloroform (15ml) was added dropwise a solution of bromine (0.3ml) in chloroform (5ml) and the resulting mixture was stirred for 3 hours. The solvent was removed by evaporation to give a gum which was purified by flash column chromatography on silica, eluting with ethyl acetate/hexane (2:3 v/v) to give dimethyl 4-[(2'-bromopropionyl)phenylene-1,2-dioxy)diacetate (1.95g), which solidified on standing: NMR (d_6DMSO) δ 1.75(d,3H), 3.7(s,6H), 4.9(s,2H), 4.95(s,2H), 5.8(q,1H), 7.05(d,1H), 7.5(d,1H), 7.7(dd,1H); m/e 389/391 (M+H)$^+$ Br pattern.

EXAMPLE 44: 4-[2-[(4-pyridyl)piperazin-1-yl]-2-methyl]acetyl-1,2-diphenoxydiacetic acid

In a similar manner to Example 40, but starting from the product of Example 43 was prepared the title compound: NMR (d_6DMSO) δ 1.4(d,3H), 3.0-3.2(m,4H), 3.75-3.9(m,4H), 4.75.5.0(m,1H), 4.8(s,2H), 4.85(s,2H), 7.05(d,1H), 7.25(d,2H), 7.55(d,1H), 7.75(dd,1H), 8.3(d,2H); m/e 444(M+H)$^+$. Calculated for $C_{22}H_{25}N_3O_7$.2.25CF_3COOH.H_2O C, 44.3; H, 4.1; N, 5.85; TFA, 35.7. Found C, 44.2; H, 3.9; N, 5.7; TFA, 36.2.

EXAMPLE 45: Methyl 2-S-(n-butylsulphonylamino)-3-[4-[3-[1-(4-pyridyl)-piperidin-4-yl]propoxy]phenyl]propionate.

Using a procedure similar to that described in Example 21, but starting from the appropriate amino ester, the title compound was prepared; NMR(d_6DMSO): 0.75(t,3H), 1.0-1.44(m,8H), 1.44-1.64(m,1H), 1.75(brd,4H), 2.5-3.02(m,6H), 3.64(s,3H), 3.85-4.1(m,5H), 6.81(d,2H), 6.84(d,2H), 7.19(d,2H), 7.78(d,1H), 8.12(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 518 (M+H)$^+$.

The starting material was prepared using similar procedures to those described in Example 19. There was thus prepared the following intermediates (i) and (ii) which were themselves prepared starting from 4-(4-hydroxypropylpiperidin-1-yl) pyridine(iii).

(i) Methyl 2-S-(benzyloxycarbonylamino)-3-[4-[3-[1-(4-pyridyl)piperidin-4-yl] propoxy]phenyl]propionate; NMR(d_6DMSO): 1.18-1.24(m,2H), 1.3-1.43(m,2H), 1.44-1.65(m,1H), 1.65-1.83(m,4H), 2.7-2.88(m,3H), 2.96(dd,1H), 3.61(s,3H), 3.92(t,4H), 4.14-4.25(m,1H), 4.98(s,2H), 6.8(d,2H), 6.82(d,2H), 7.14(d,2H), 7.2-7.4(m,5H), 7.74(d,1H), 8.12(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 532(M+H)$^+$.

(ii) Methyl 2-S-amino-3-[4-[3-[1-(4-pyridyl)piperidin-4-yl]propoxy]phenyl] propionate; NMR(d_6DMSO): 1.03-1.2(m,2H), 1.28-1.40(m,2H), 1.42-1.62(m,1H), 1.64-1.80(m,4H), 2.65-2.9(m,4H), 3.58(s,3H), 3.45-3.6(m,1H), 3.85-3.98(m,4H), 6.78(d,2H), 6.8(d,2H), 7.06(d,2H), 8.11(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 398(M+H)$^+$.

(iii) 4-(4-Hydroxypropylpiperidin-1-yl)pyridine.

A solution of N-(2-carbamoylethyl)-4-cyanopyridinium chloride (2.1g) in water (5ml) was added dropwise to a stirred mixture of 4-hydroxypropylpiperidine (2.4g), water (10ml) and 2.5M sodium hydroxide solution (4.6ml) cooled in an ice-bath. The mixture was stirred at 0-5°C for 1 hour. 2.5M sodium hydroxide solution (7ml) was added and the mixture heated at reflux for 3 hours. The mixture was cooled in an ice-bath and gummy solid separated out. The aqueous layer was decanted off and the gummy solid dissolved in dichloromethane (75ml). The solution was washed with saturated sodium chloride solution (10ml) and dried ($MgSO_4$). The solvent was removed by evaporation to give a gummy solid (880mg) which on trituration with ether gave a solid; NMR(d_6DMSO): 1.0-1.35(m,4H), 1.35-1.6(m,3H), 1.7(dd,2H), 2.70-2.88(dt,2H), 3.38(t,2H), 3.89(brd,2H), 4.35(brs,1H), 6.78(d,2H), 8.1(d,2H); mass spectrum(CI$^+$): 221(M+H)$^+$.

EXAMPLE 46: 2-S-(n-butylsulphonylamino)-3-[4-[3-[1-(4-pyridyl)piperidin-4-yl]propoxy]phenyl]propionic acid.

Using a similar procedure to that described in Example 20, but starting from the product of Example 45, the title compound was obtained as an amorphous solid; NMR(d_6DMSO/CD_3CO_2D): 0.73(t,3H), 1.0-1.5(m,8H), 1.55-1.85(m,5H), 2.54-2.78(m,3H), 2.9-3.2(m,3H), 3.8-3.98(m,3H), 4.15(brd,2H), 6.8(d,2H), 7.09(d,2H), 7.15(d,2H), 8.1(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 504(M+H)$^+$; microanalysis found C,60.3; H,7.2; N,7.9%; $C_{26}H_{37}N_3O_5S$.H_2O requires C,59.9; H,7.5; N,8.1%.

EXAMPLE 47: Methyl 2-S-(butylsulphonylamino)-3-[4-[4-[1-(4-pyridyl)piperidin-4-yl]butoxy]phenyl]propionate.

Using a similar procedure to that described in Example 21, but starting from the appropriate amino ester, the title compound was prepared; NMR(CDCl$_3$): 0.87(t,3H), 1.14-1.4(m,6H), 1.42-1.7(m,5H), 1.7-1.9(m,4H), 2.7-3.18(m,6H), 3.78(s,3H), 3.9(brd,2H), 3.93(t,2H), 4.32(brs,1H), 4.82(brs,1H), 6.66(d,2H), 6.83(d,2H), 7.09(d,2H), 8.22(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 532 (M+H)$^+$.

The starting material was prepared using similar procedures to those described in Example 19 and 45(iii). There was thus prepared the following intermediates:-

(i) 4-(4-hydroxybutylpiperidin-1-yl)pyridine; NMR(d$_6$DMSO): 0.97-1.58(m,9H), 1.7(dd,2H), 2.78(dt,2H), 3.38(m,2H), 3.88(brd,2H), 4.29(t,1H), 6.78(d,2H), 8.10(d,2H); mass spectrum(CI$^+$): 235(M+H)$^+$.

(ii) Methyl 2-S-(benzylcarbonylamino)-3-[4-[4-[1-(4-pyridyl)piperidin-4-yl]butoxy]phenyl]propionate; NMR(d$_6$DMSO): 1.0-1.35(m,4H), 1.35-1.60(m,3H), 1.62-1.80(m,4H), 2.8(dt,3H), 2.96(dd,1H), 3.62(s,3H), 3.85-3.97(m,4H), 4.15-4.28(m,1H), 4.99(s,2H), 6.78(d,2H), 6.81(d,2H), 7.13(d,2H), 7.2-7.4(m,5H), 7.74(d,1H), 8.11(d,2H); mass spectrum(CI$^+$): 546(M+H)$^+$.

(iii) Methyl 2-S-amino-3-[4-[4-[1-(4-pyridyl)-piperidin-4-yl]butoxy]phenyl]propionate; NMR(d$_6$DMSO): 1.05-1.35(m,4H), 1.35-1.58(m,3H), 1.6-1.8(m,4H), 2.65-2.9(m,4H), 3.51(t,1H), 3.58(s,3H), 3.8-3.98(m,4H), 6.78(dd,2H), 6.81(d,2H), 7.05(d,2H), 8.1(dd,2H); mass spectrum(CI$^+$): 412(M+H)$^+$.

EXAMPLE 48: 2-S-(n-butylsulphonylamino)-3-[4-[4-[1-(4-pyridyl)piperidin-4-yl]butoxy]phenyl]propionic acid.

Using a similar procedure to that described in Example 20 but starting from the product of Example 47, the title compound was obtained as an amorphous solid; NMR(d$_6$DMSO): 0.78(t,3H), 1.0-1.6(m,11H), 1.6-1.82(brt,4H), 2.5-3.04(m,6H); 3.8-4.0(m,5H), 6.8(m,4H), 7.19(d,2H), 8.1(brd,2H); mass spectrum(+ve FAB,MeOH/NBA): 518(M+H)$^+$; microanalysis found C,62.4; H,7.8; N,7.9%; C$_{27}$H$_{39}$N$_3$O$_5$S requires C,62.6; H,7.6; N,8.1%.

EXAMPLES 49-51:

Using a procedure similar to that described in Example 21, but starting from the appropriate substituted sulphonyl chloride and methyl 2-S-amino-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionate there was obtained the following compounds:-

Example 49: Methyl 2-S-(methylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionate NMR(d$_6$DMSO): 1.08-1.34(m,2H), 1.6-1.85(m,5H), 2.6(s,3H), 2.7-3.0(m,4H), 3.63(s,3H), 3.84-4.2(m,5H), 6.80(d,2H), 6.85(d,2H), 7.18(d,2H), 8.12(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 462(M+H)$^+$.

Example 50: Methyl 2-S-(benzylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionate NMR(d$_6$DMSO): 1.05-1.28(m,2H), 1.57-1.82(m,5H), 2.68-2.95(m,4H), 3.58(s,3H), 3.8-4.15(m,7H), 6.79(d,2H), 6.88(d,2H), 7.12(d,2H), 7.17(m,2H), 7.3(m,3H), 7.79(brd,1H), 8.1(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 538(M+H)$^+$.

Example 51: Methyl 2-S-(4-methylphenylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionate NMR(d$_6$DMSO): 1.1-1.33(m,2H), 1.6-1.88(m,5H), 2.35(s,3H), 2.6-2.75(dd,1H), 2.75-2.92(m,3H), 3.38(s,3H), 3.8-4.1(m,5H), 6.76(d,2H), 6.81(d,2H), 7.0(d,2H), 7.28(d,2H), 7.47(d,2H), 8.12(d,2H), 8.32(d,1H); mass spectrum(+ve FAB, MeOH/NBA): 538(M+H)$^+$.

EXAMPLES 52-54:

Following the method of Example 20, but using the products of Examples 49-51, there vas obtained the following compounds:-

EXAMPLE 52: 2-S-(Methylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionic acid NMR(d$_6$DMSO): 1.05-1.35(m,2H), 1.6-1.95(m,5H), 2.61(s,3H), 2.65-3.1(m,4H), 3.88-4.1(m,5H), 6.84(d,2H), 6.9(d,2H), 7.18(d,2H), 8.14(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 448(M+H)$^+$.

EXAMPLE 53: 2-S-(Benzylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionic acid NMR(d$_6$DMSO/CD$_3$CO$_2$D): 1.07-1.35(m,2H), 1.60-1.88(m,5H), 2.7-3.2(m,4H), 3.85-4.25(m,7H), 6.87(d,2H), 7.1(d,2H), 7.13-7.45(m,7H), 8.15(d,2H); mass spectrum(+ve FAB,MeOH/NBA): 524(M+H)$^+$; microanalysis found

C,61.8; H,6.8; N,7.6%; $C_{28}H_{33}N_3O_5S.H_2O$ requires C,62.1; H,6.5; N,7.8%.

EXAMPLE 54: Lithium 2-S-(4-methylphenylsulphonylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionate NMR(d_6DMSO/CD_3CO_2D): 1.15-1.38(m,2H), 1.67-1.78(m,2H), 1.82-2.0(m,3H), 2.36(s,3H), 2.65-2.8(dd,1H), 2.85-2.95(dd,1H), 3.14(t,2H), 3.78(m,1H), 4.0(t,2H), 4.18(d,2H), 6.77(d,2H), 7.04(d,2H), 7.11(d,2H), 7.24(d,2H), 7.51(d,2H), 8.15(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 536(M+Li)$^+$; microanalysis found C,63.2; H,6.5; N,7.9%; $C_{28}H_{32}N_3O_5SLi$ requires C,63.5; H,6.1; N,7.9%.

EXAMPLE 55: Methyl 2-S-(pentanoylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionate.

Valeryl chloride (0.25ml) was added dropwise to a solution of methyl 2-S-amino-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionate (640mg) and triethylamine (0.7ml) in dichloromethane (17ml) at ambient temperature. The reaction mixture was stirred for 5 hours and then diluted with dichloromethane (20ml) and washed with water (20ml), saturated sodium chloride solution (10ml) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by flash chromatography eluting with methanol/dichloromethane (1:9v/v) to give the title compound (660mg) as a gum; NMR(d_6DMSO): 0.81(t,3H), 1.05-1.3(m,4H), 1.3-1.45(m,2H), 1.60-1.85(m,5H), 2.04(t,2H), 2.7-3.0(m,4H), 3.6(s,3H), 3.92(d,2H), 3.99(t,2H), 4.35-4.48(m,1H), 6.8(d,2H), 6.83(d,2H), 7.11(d,2H), 8.12(d,2H), 8.18(d,1H); mass spectrum(+ve FAB,MeOH/NBA): 468(M+H)$^+$.

EXAMPLE 56: Methyl 2-S-(pentanoylamino)-3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]propionate.

Using a procedure similar to that described in Example 55, but starting from the appropriate amino ester, the title compound was prepared, NMR(d_6DMSO): 0.8(t,3H), 1.05-1.45(m,6H), 1.83(dd,2H), 1.9-2.1(m,1H), 2.04(t,2H), 2.7-3.0(m,4H), 3.59(s,3H), 3.82(d,2H), 3.96(d,2H), 4.35-4.48(m,1H), 6.80(d,2H), 6.83(d,2H), 7.10(d,2H), 8.12(d,2H), 8.17(d,1H); mass spectrum(+ve FAB, MeOH/NBA): 454(M+H)$^+$.

EXAMPLE 57: 2-S-(Pentanoylamino)-3-[4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenyl]propionic acid.

Using a procedure similar to that described in Example 20, but starting from the product of Example 55, the title compound was prepared, NMR(d_6DMSO): 0.8(t,3H), 1.08-1.3(m,4H), 1.3-1.45(m,2H), 1.6-1.87(m,5H), 2.05(t,2H), 2.7-3.05(m,4H), 3.9-4.05(m,4H), 4.3-4.43(m,1H), 6.82(d,2H), 6.85(d,2H), 7.11(d,2H), 7.97(d,1H), 8.12(brd,2H); mass spectrum(+ve FAB, MeOH/NBA): 454(M+H)$^+$; microanalysis found C,63.1; H,7.8; N,8.3%; $C_{26}H_{35}N_3O_4.2H_2O$ requires C,63.8; H,8.0; N,8.6%.

EXAMPLE 58: 2-S-(Benzyloxycarbonylamino)-3-[4-[2-[1-(4-pyridyl) piperidin-4-yl]ethoxy]phenyl]propionic acid.

Using a procedure similar to that described in Example 20, but starting from the product of Example 35, step (i), the title compound was prepared, NMR(d_6DMSO): 1.1-1.35(m,2H), 1.6-1.9(m,5H), 2.65-3.1(m,4H), 3.85-4.2(m,5H), 4.96(s,2H), 6.75-6.9(m,4H), 7.14(d,2H), 7.2-7.35(m,5H), 7.5(d,1H), 8.1(d,2H); mass spectrum(+ve FAB, MeOH/NBA): 504(M+H)$^+$.

EXAMPLE 59: Methyl-2-S-(n-butylsulphonylamino)-3-[3-(N-methyl-N-4-pyridyl)aminopropoxy]phenylpropionate.

Using a procedure similar to that described in Example 19, but starting from methyl 2-S-amino-3-[3-(N-methyl-N-4-pyridyl)aminopropoxy]phenylpropionate, the title compound was prepared, NMR($CDCl_3$): 0.89(t,3H), 1.25-1.4(m,2H), 1.55-1.75(m,2H), 2.0-2.15(m,2H), 2.80(dd,2H), 2.9-3.15(m,2H), 3.05(s,3H), 3.63(t,2H), 3.77(s,3H), 3.95(t,2H), 4.28-4.38(m,1H), 6.57(d,2H), 6.80(d,2H), 7.10(d,2H), 8.14(d,2H); mass spectrum (CI$^+$): 464(M+H)$^+$. The necessary starting material was prepared as follows:-

(i) Using a procedure similar to that described in Example 19, step (i), but starting from N-methyl-N-(4-pyridyl)aminopropanol and N-t-butyloxycarbonyl-S-tyrosine methyl ester, there was obtained, methyl 2-S-(t-butyloxycarbonylamino)-3-[3-N-methyl-N-(4-pyridyl)aminopropoxy]phenyl propionate, as a gum, NMR($CDCl_3$): 1.43(s,9H), 2.0-2.15(m,2H), 3.04(s,3H), 2.95-3.10(m,2H), 3.62(t,2H), 3.73(s,3H), 3.98(t,2H), 4.54(brd,1H), 4.98(brd,1H), 6.56(d,2H), 6.80(d,2H), 7.04(d,2H), 8.17(d,2H).

(ii) The product from step (i) (500mg) and 5M methanolic hydrochloric acid solution (4ml) was stirred at ambient temperature for 16 hours. The solvent was evaporated to give the corresponding amino compound as the dihydrochloride salt which was used without further purification.

EXAMPLE 60: 2-S-(n-Butylsulphonylamino)-3-[3-(N-4-pyridyl-N-methyl)aminopropoxy]phenyl propionic acid

Using a procedure similar to that described in Example 20, but starting from the product of Example 59, the title compound was prepared, NMR(d_6DMSO/CD_3CO_2D): 0.8(t,3H), 1.1-1.28(m,2H), 1.28-1.55(m,2H), 2.0-2.15(m,2H), 2.6-2.8(m,3H), 2.93-3.08(dd,1H), 3.18(s,3H), 3.75(t,2H), 3.9-4.05(m,3H), 6.86(d,2H), 7.0(d,2H), 7.2(d,2H), 8.15(d,2H); mass spectrum (+ve FAB,MeOH/NBA): 450(M+H)$^+$; microanalysis found C,53.9; H,6.9; N,8.4%; $C_{22}H_{31}N_3O_5S.2H_2O$ requires C,54.4; H,7.2; N,8.6%.

EXAMPLE 61: Methyl 3-(n-butylsulphonylamino)-3-[4-[1-(4-pyridyl) piperidin-4-yl]methoxyphenyl]propionate.

Using a procedure similar to that described in Example 19, but starting from methyl 3-amino-3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]propionate, dihydrochloride, the title compound was prepared; NMR($CDCl_3$): 0.84(t,3H), 1.2-1.4(m,2H), 1.4-1.55(m,2H), 1.55-1.75(m,2H), 1.97(brd,2H), 2.02-2.2(m,1H), 2.65-2.85(m,2H), 2.88(d,2H), 3.0(dt,2H), 3.67(s,3H), 3.84(d,2H), 4.0(brd,2H), 4.85(q,1H), 5.40(d,1H), 6.71(d,2H), 6.86(d,2H), 7.27(d,2H), 8.25(d,2H); mass spectrum(+ve FAB,MeOH/NBA): 490(M+H)$^+$.
The starting material was prepared as follows:-

(i) Thionyl chloride (4.3ml) was added to methanol (50ml) cooled in an ice-salt bath. 3-Amino-3-(4-hydroxyphenyl)propionic acid (9.7g) was added and the mixture allowed to reach ambient temperature and then refluxed for 2 hours. The solvent was removed by evaporation in vacuo to give a gummy solid (12.8g) which was used without further purification. A solution of di-t-butyldicarbonate (5.8g) in dichloromethane (50ml) was added to a stirred mixture of the gummy solid (5.75g) and potassium hydrogen carbonate (6.2g) in water (20ml). The mixture was stirred at ambient temperature for 4 hours. The organic layer was separated and washed with water (10ml), 1M hydrochloric acid solution (10ml), saturated sodium hydrogen carbonate solution (10ml), water (10ml) and dried ($MgSO_4$). The solvent was evaporated to give methyl 3-(t-butyloxycarbonylamino)-3-(4-hydroxyphenyl)propionate as a solid; m.p. 119-120°C; NMR(d_6DMSO) : 1.34(s,9H), 2.54-2.78(m,2H), 3.53(s,3H), 4.7-4.9(q,1H), 6.67(d,2H), 7.08(d,2H), 7.28(brd,1H), 9.24(brs,1H).

(ii) Using a procedure similar to that described in Example 19, step (i), but using the product of step (i), methyl 3-(t-butyloxycarbonylamino)-3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]propionate was prepared as a gum; NMR($CDCl_3$): 1.33-1.55(m,2H), 1.44(s,9H), 1.95(brd,2H), 1.95-2.15(m,1H), 2.7-3.0(m,4H), 3.61(s,3H), 3.80(d,2H), 3.95(brd,2H), 4.95-5.1(m,1H), 5.25-5.40(m,1H), 6.68(d,2H), 6.85(d,2H), 7.2(d,2H), 8.25(d,2H).

(iii) The product of step (ii) (550mg) and 5M methanolic hydrochloric acid solution (4ml) was stirred at ambient temperature for 18 hours. The solvent was evaporated to give methyl 3-amino-3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl] propionate dihydrochloride as a foam; NMR(d_6DMSO/CD_3CO_2D): 1.23-1.45(m,2H), 1.92(brd,2H), 2.05-2.25(m,1H), 3.0-3.25(m,4H), 3.52(s,3H), 3.85(d,2H), 4.2(brd,2H), 4.54(t,1H), 6.92(d,2H), 7.1(d,2H), 7.39(d,2H), 8.10(d,2H).

EXAMPLE 62: 3-(n-Butylsulphonylamino)-3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]propionic acid.

Using a procedure similar to that described in Example 20, but using the product of Example 61, the title compound was prepared; NMR(d_6DMSO/CD_3CO_2D): 0.78(t,3H), 1.05-1.3(m,2H), 1.3-1.57(m,4H), 1.98(brd,2H), 2.1-2.33(m,1H), 2.45-2.85(m,4H), 3.25(t,2H), 3.89(d,2H), 4.25(brd,2H), 4.68(t,1H), 6.90(d,2H), 7.14(d,2H), 7.33(d,2H), 8.14(d,2H); mass spectrum(+ve FAB,MeOH/NBA): 490(M+H)$^+$.

EXAMPLE 63: Methyl 3-(4-methylphenylsulphonylamino)-3-[4-[1-(4-pyridyl)-piperidin-4-yl]methoxyphenyl]propionate.

Using a procedure similar to that described in Example 19, but starting from the product of Example 61, step (iii) and p-toluenesulphonyl chloride, the title compound was prepared; NMR($CDCl_3$): 1.34-1.55(m,2H), 1.95(d,2H), 2.0-2.2(m,1H), 2.38(s,3H), 2.62-3.05(m,4H), 3.55(s,3H), 3.78(d,2H), 3.96(d,2H), 4.65(m,1H), 5.65(brs,1H), 6.7(d,2H), 6.72(d,2H), 7.05(d,2H), 7.2(d,2H), 7.65(d,2H), 8.25(d,2H); mass spectrum(+ve FAB,MeOH/NBA): 524(M+H)$^+$.

EXAMPLE 64: Methyl 2-R-(n-butylsulphonylamino)-3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]propionate.

Using a procedure similar to that described in Example 19, but starting from methyl 2-R-amino-3-[4-[1-(4-pyridyl)piperidin-4-yl]-methoxyphenyl]propionate, the title compound was prepared; NMR($CDCl_3$): 0.88(t,3H), 1.2-1.7(m,6H), 1.96(d,2H), 2.0-2.2(m,1H), 2.7-2.83(m,2H), 2.85-3.15(m,4H), 3.77(s,3H), 3.79(d,2H), 3.96(d,2H), 4.32(m,1H), 4.85(brd,1H), 6.7(d,2H), 6.83(d,2H), 7.08(d,2H), 8.25(brd,2H); mass spectrum(+ve FAB,MeOH/NBA): $490(M+H)^+$.

The necessary starting material was prepared as follows:-

(i) Using a similar procedure to that described in Example 19, step (i), but starting from N-t-butyloxycarbonyl-S-tyrosine methyl ester, there was obtained, methyl 2-R-(t-butyloxycarbonylamino)-3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]propionate as a gum, NMR($CDCl_3$): 1.43(s,9H), 1.36-1.55(m,2H), 1.96(brd,2H), 2.0-2.15(m,1H), 2.95(dt,2H), 3.03(d,2H), 3.71(s,3H), 3.81(d,2H), 3.95(brd,2H), 4.52(brd,1H), 4.95(brd,1H), 6.70(d,2H), 6.80(d,2H), 7.01(d,2H), 8.24(d,2H).

(ii) Using a similar procedure to that described in Example 59, step (ii), but starting from the product obtained in step (i), there was obtained, methyl 2-R-amino-3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]propionate dihydrochloride as a foam, NMR(d_6DMSO/CD_3CO_2D): 1.26-1.48(m,2H), 1.96(brd,2H), 2.1-2.3(m,1H), 3.09(dd,2H), 3.21(t,2H), 3.70(s,3H), 3.84(d,2H), 4.15-4.3(m,3H), 6.88(d,2H), 7.14(m,4H), 8.14(d,2H).

EXAMPLE 65: 2-R-(n-Butylsulphonylamino)-3-[4-[1-(4-pyridyl)piperidin-4-yl]-methoxyphenyl]propionic acid.

Following the method of Example 20, but using the product of Example 64, the title compound was prepared; NMR(d_6DMSO): 0.75(t,3H), 1.03-1.45(m,6H), 1.87(d,2H), 1.95-2.2(m,1H), 2.45-2.78(m,3H), 2.88-3.08(m,3H), 3.82(d,2H), 3.8-3.95(m,1H), 4.05(brd,2H), 6.84(d,2H), 6.92(d,2H), 7.18(d,2H), 8.13(brs,2H); mass spectrum(-ve FAB,MeOH/NBA): $474(M-H)^-$; microanalysis found C,55.1; H,6.8; N,7.8%; $C_{24}H_{33}N_3O_5S.2.5H_2O$ requires C,55.4; H,7.3; N,8.1%.

EXAMPLE 66 : Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-2,6-dichlorophenoxyacetate.

Prepared in a similar manner to Example 5, but starting from methyl 4-bromoacetyl-2,6-dichlorophenoxyacetate, however stirring for only 6 hours and purification by flash chromatography on silica, eluting first with dichloromethane then successively 2,3,4 and 5% v/v methanol/dichloromethane. Concentration of the fractions in vacuo and recrystallisation of the residue from methanol gave the title compound in 24% yield as a pale orange solid: m.p. 149-150°C; NMR (d_6DMSO) δ 8.14 (2H, d), 8.06 (2H, s), 6.81 (2H, d), 4.82 (2H, s), 4.05 (0.5H, b), 3.94 (2H, s), 3.73 (3H, s), 3.32 (4H, t), 3.18 (1.5H, s), 2.64 (4H, t); m/e 438 $(M+H)^+$, 2xCl pattern;
calculated for $C_{20}H_{21}Cl_2N_3O_4.0.5CH_3OH$: C, 54.1; H, 5.1; N, 9.2. found: C, 53.7; H, 5.4; N, 8.9%.
The starting material was prepared as follows:-

(i) Sodium hydride (50% w/w dispersion in mineral oil, 1.32 g) was treated under argon with repeated washes of hexane. The oil-free residue was suspended in dry DMF (10 ml) and, with stirring and cooling (ice-bath), a solution of 3,5-dichloro-4-hydroxyacetophenone (5.13 g) in dry DMF (15 ml) was added dropwise. Stirring was continued for 30 minutes when methyl bromoacetate (3.06 ml) was added dropwise and stirring was continued for a further 18 hours at ambient temperature. The reaction mixture was added to water, the mixture was extracted twice with ethyl acetate, the organic phases dried ($MgSO_4$), filtered and then evaporated. The residue, after recrystallisation from hexane (250 ml), gave methyl 4-acetyl-2,6-dichlorophenoxyacetate, 4.25 g, as white crystals: NMR (d_6DMSO) δ 8.00 (2H, s), 4.80 (2H, s), 3.73 (3H, s), 2.59 (3H, s).
(ii) A solution of bromine (0.77 ml) in chloroform (10 ml) was added dropwise over 15 minutes to a stirred solution of the product from step (i) (4.16 g) in chloroform (40 ml) at 25°C. The temperature was raised to 40°C for 1 hour and then stirring continued for a further 18 hours at ambient temperature. The solvent was removed in vacuo and the residual oil purified by flash chromatography on silica, eluting with dichloromethane, to give a crystalline solid. Recrystallisation from methanol gave methyl 4-bromoacetyl-2,6-dichlorophenoxyacetate, 1.88 g, as white crystals: m.p. 89-90°C; NMR (d_6DMSO) δ 8.06 (2H, s), 4.93 (2H, s), 4.82 (2H, s), 3.72 (3H, s); m/e 355/357 $(M+H)^+$, 1 Br pattern; calculated for $C_{11}H_9BrCl_2O_4$: C, 37.1; H, 2.3. found: C, 36.8; H, 2.4%.

EXAMPLE 67: Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-3-methylphenoxyacetate.

In a similar manner to Example 5, but starting from methyl 4-bromoacetyl-3-methylphenoxyacetate and vith purifi-

cation by flash chromatography on silica, eluting with 0 to 5% v/v methanol/dichloromethane, and then by flash chromatography on neutral alumina, eluting first vith dichloromethane and then 1% v/v methanol/dichloromethane there was obtained the title compound in 9% yield as a yellow oil: NMR (d_6DMSO) δ 8.15 (2H, d), 7.38 (1H, d), 6.82 (4H, m), 4.88 (2H, s), 3.75 (2H, s), 3.71 (3H, s), 3.32 (4H, t), 2.61 (4H, t), 2.43 (3H, s), m/e 384 $(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4.0.5H_2O.0.1\ CH_2Cl_2$: C, 63.1; H, 6.5; N, 10.5. found: C, 62.6; H, 6.6; N, 10.2%.
The starting material was prepared as follows:-

(i) A mixture of 4-hydroxy-2-methylacetophenone (4.8 g), anhydrous potassium carbonate (5.3 g) and methyl bromoacetate (3.55 ml) in anhydrous acetone (100 ml) was stirred for 2 days. The mixture, after filtration and evaporation of the solvent, gave methyl 4-acetyl-3-methylphenoxyacetate, 6.6 g, as a crystalline solid: m.p. 49-50°C; NMR (d_6DMSO) δ 7.84 (1H, d), 6.83 (2H, m), 4.87 (2H, s), 3.71 (3H, s), 2.50 (3H, s), 2.45 (3H, s).

(ii) Prepared in a similar manner to Example 76 step (ii), but starting from the product of (i) above and purification by flash chromatography on silica eluting with 10 to 17.5% v/v ethyl acetate/hexane. Recrystallisation from ethanol gave methyl 4-bromoacetyl-3-methylphenoxyacetate, in 35% yield, as white needles: NMR (d_6DMSO) δ 7.90 (1H, d), 6.90 (1H, s), 6.88 (1H, d), 4.90 (2H, s), 4.78 (2H, s), 3.71 (3H, s), 2.43 (3H, s).

EXAMPLE 68 : Mixture of methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-2-methylphenoxyacetate and ethyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-2-methylphenoxyacetate (3:2).

A mixture of methyl 4-acetyl-2-methylphenoxyacetate (3.33 g) and cupric bromide (7.0 g) in ethyl acetate (50 ml) was heated on a steam bath for 18 hours. After filtration, the solvent was evaporated and the residual solid purified by flash chromatography on silica eluting with 10% v/v ethyl acetate/hexane to give an off-white solid. Recrystallisation from ethanol gave white needles, 2.37 g, shown by NMR (d_6DMSO) to be a mixture of methyl 4-bromoacetyl-2-methylphenoxyacetate and ethyl 4-bromoacetyl-2-methylphenoxyacetate which was used without further purification. The mixture (2.25 g) was added portionwise to a stirred solution of 1-(4-pyridyl)piperazine (2.45 g) in acetonitrile (50 ml) and the mixture stirred for 18 hours. The reaction mixture was filtered and the filtrate evaporated to give an orange oil. Purification by flash chromatography on silica eluting with dichloromethane then 1 to 3% v/v methanol/dichloromethane gave the title mixture of compounds, 0.87 g, as a solid: m.p. 136-138°C; NMR (d_6DMSO) δ 8.04 (2H, d), 7.85 (1H, d), 7.82 (1H, s), 6.95 (1H, d), 6.81 (2H, d), 4.96 and 4.93 (2H, s,s), 4.18 (0.7H, q), 3.84 (2H, s), 3.72 (1.7H, s), 3.30 (4H, t), 2.60 (4H, t), 2.25 (3H, s), 1.21 (1.3H, t), [Ratio of methyl to ethyl ester 3:2]; m/e 384 $(M+H)^+$ for methyl ester, 398 $(M+H)^+$ for ethyl ester; calculated for $C_{21}H_{25}N_3O_4$: $C_{22}H_{27}N_3O_4$ (3:2): C, 66.1; H, 6.6; N, 10.8. found: C, 65.8; H, 6.7; N, 10.5%.
The starting material was prepared as follows:-

(i) A mixture of 4-hydroxy-3-methylacetophenone (5 g), methyl bromoacetate (3.70 ml) and anhydrous potassium carbonate (5.52 g) in acetone (100 ml) was stirred for 66 hours. The mixture was filtered and the filtrate evaporated to give an oil which crystallised on standing giving methyl 4-acetyl-2-methylphenoxyacetate, 7.2 g: m.p. 51-53°C; NMR (d_6DMSO) δ 7.79 (1H, s), 7.77 (1H, d), 6.94(1H,d), 4.93 (2H, s), 3.71 (3H, s), 2.50 (3H, s + DMSO), 2.24 (3H, s).

EXAMPLE 69 : Mixture of methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-3-methoxyphenoxyacetate and ethyl4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-3-methoxyphenoxyacetate (3:1).

In a similar manner to Example 68, but starting from methyl 4-acetyl-3-methoxyphenoxyacetate there aas prepared, after flash chromatography on silica eluting with dichloromethane, a mixture of methyl 4-bromoacetyl-3-methoxyphenoxyacetate and ethyl 4-bromoacetyl-3- methoxyphenoxyacetate in 60% yield: m.p. 84-86°C. Treatment of this mixture, as in Example 68, followed by chromatography on silica eluting with 1 to 5% v/v methanol/dichloromethane gave the title mixture of compounds in 24% yield as a solid: NMR (d_6DMSO) δ 8.13 (2H, d), 7.63 (1H, d), 6.80 (2H, d), 6.67 (1H, d), 6.59 (1H, dd), 4.90 and 4.88 (2H, 2s), 4.18 (0.5, q), 3.88 (3H, s), 3.75 (2H, s), 3.71 (2.3H, s), 3.32 (4H, t), 2.62 (4H, t), 1.22 (0.7 H, t) [Ratio of methyl to ethyl ester 3:1]; m/e 400 $(M+H)^+$ for methyl ester, 414 $(M+H)^+$ for ethyl ester; calculated for $C_{21}H_{25}N_3O_5$: $C_{22}H_{27}N_3O_5$ (3:1): C, 63.3; H, 6.5; N, 10.4. found C, 63.1; H, 6.5; N, 10.3%.
The starting material was prepared as follows:-

(i) In a similar manner to Example 68 step (i), but starting from 4-hydroxy-2-methoxy-acetophenone there was obtained, after evaporation of the solvent and trituration with diethyl ether, methyl 4-acetyl-3-methoxyphenoxyacetate in 91% yield as a white solid: m.p. 95-96°C; NMR (d_6DMSO) δ 7.64 (1H, d), 6.70 (1H, d), 6.60 (1H, dd), 4.91 (2H, s), 3.89 (3H, s), 3.72 (3H, s), 2.49 (3H, s).

EXAMPLE 70 : Mixture of dimethyl 2,2'-[4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-phenylene-1,3-dioxy]diacetate and diethyl 2,2'-[4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenylene-1,3-dioxy]diacetate(1:1).

In a similar manner to Example 68, but starting from dimethyl 2,2'-[(4-acetyl)phenylene-1,3-dioxy]diacetate there was prepared, after flash chromatography on silica eluting with dichloromethane, a mixture of dimethyl 2,2'-[(4-bromoacetyl)phenylene-1,3-dioxy]diacetate and diethyl 2,2'-[(4-bromoacetyl)phenylene-1,3-dioxy] diacetate in 28% yield. Treatment of the mixture, as in Example 68, followed by chromatography on silica eluting with 1 to 5% v/v methanol/dichloromethane gave the title mixture of compounds in 44% yield as a solid: NMR (d_6DMSO) δ 8.14 (2H, d), 7.63 (1H, d), 6.82 (2H, d), 6.65 (2H, d), 4.96 and 4.93 (2H, 2s), 4.49 and 4.47 (2H, 2s), 4.20 (2H, m), 3.91 (2H, s), 3.75 and 3.71 (3H, 2s), 3.32 (4H + H_2O), 2.61 (4H, t), 1.23 (3H, m) [Ratio of methyl to ethyl esters 1:1]; m/e 458 $(M+H)^+$ for dimethyl ester and 486 $(M+H)^+$ for diethyl ester; calculated for $C_{23}H_{27}N_3O_7$: $C_{25}H_{31}N_3O_7$ (1:1). H_2O:C,60.0; H, 6.3; N, 8.7. found: C, 60.3; H, 6.2; N, 8.5%.

The starting material was prepared as follows:-

(i) In a similar manner to Example 68 step (i), but starting from 2,4-dihydroxy acetophenone and using 2.4 equivalents of methyl bromoacetate and 2.4 equivalents of anhydrous potassium carbonate there was obtained, after evaporation and trituration with diethyl ether/hexane (1:1 v/v), dimethyl 2,2'- [(4-acetyl)phenylene-1,3-dioxy]diacetate in 82% yield as a white solid: m.p. 119-120°C; NMR (d_6DMSO) δ 7.64 (1H, d), 6.56 (2H, m), 4.99 (2H, s), 4.90 (2H, s), 3.73 (3H, s), 3.71 (3H, s), 2.57 (3H, s).

EXAMPLE 71 : 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]-2,6-dichlorophenoxyacetic acid, dihydrochloride.

A solution of the product of Example 66 (190 mg) in dioxane (1.7 ml) was treated with 1N hydrochloric acid (1.7 ml) and the mixture heated at 100°C for 1.5 hours. The mixture was cooled, diluted with water and freeze-dried. The solid residue, on treatment with a small volume of ethanol, gave the title compound, 120 mg, as a white solid: m.p. 174-176°C; NMR (D_2O) δ 8.42 (2H, d), 8.26 (2H, s), 7.41 (2H, d), 5.24 (2H, s), 4.98 (2H, s), 4.34 (4H, t), 3.90 (4H, t); m/e 424 $(M+H)^+$, 2xCl pattern; calculated for $C_{19}H_{19}Cl_2N_3O_4.2HCl.H_2O$: C, 44.4; H, 4.5; N, 8.2. found: C, 44.8; H, 4.2; N, 8.1%.

EXAMPLES 72 to 75

In a similar manner to Example 71, but starting from the product of Examples 63 to 66 the following compounds were prepared:-

EXAMPLE 72 : 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]-3-methylphenoxyacetic acid, dihydrochloride.

The title compound was prepared from the product of Example 67 in 78% yield: m.p. 242-244°C; NMR (D_2O) δ 8.38 (2H, d), 8.00 (1H, d), 7.36 (2H, d), 7.14 (1H, s), 7.10 (1H, d), 5.12 (2H, s), 4.97 (2H, s), 4.30 (4H, bs), 3.84 (4H, bs), 2.75 (3H, s); m/e 370 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4$. 2HCl. $0.5H_2O$: C, 53.4; H, 5.3; N, 9.3. found C, 53.2; H, 5.8; N, 8.8%.

EXAMPLE 73 : 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]-2-methylphenoxyacetic acid, dihydrochloride.

The title compound was prepared from the product of Example 68 in 98% yield: m.p. 259 to 263°C; NMR (d_6DMSO+D_2O) δ 8.46 (2H, d), 7.95 (2H, m), 7.38 (2H, d), 7.15 (1H, d), 5.17 (2H, s), 5.00 (2H, s), 4.19 (4H, s), 3.62 (4H, s), 2.39 (3H, s); m/e 370 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4.2HCl.0.5H_2O$: C, 53.5; H, 5.8; N, 9.4. found: C, 53.6; H, 5.7; N, 9.5%.

EXAMPLE 74 : 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]-3-methoxyphenoxyacetic acid, dihydrochloride.

The title compound was prepared from the product of Example 69 in 69% yield: m.p. 168-170°C; NMR (d_6DMSO+d_4 acetic acid) δ 8.36 (2H, d), 7.93 (1H, d), 7.28 (2H, d), 6.76 (1H, d), 6.72 (1H, dd), 4.86 (2H, s), 4.78 (2H, s), 4.08 (4H, bs), 3.98 (3H, s), 3.54 (4H, bs); m/e 386 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_5.2HCl.2H_2O$: C, 48.7; H, 5.9; N, 8.5. found: C, 48.5; H, 5.7; N, 8.3%.

EXAMPLE 75 : 2,2'-[4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetylphenylene-1,3-dioxy]diacetic acid, dihydrochloride.

The title compound was prepared from the product of Example 70 in 79% yield: m.p. 257-258°C; NMR (D_2O) δ 8.39

(2H, d), 8.18 (1H, d), 7.48 (2H, d), 6.94 (1H, dd), 6.76 (1H, d), 5.18 (2H, s), 5.09 (2H, s), 5.01 (2H, s), 4.29 (4H, b), 3.34 (4H, b); m/e 430 (M+H)$^+$; calculated for $C_{21}H_{24}N_3O_7.2HCl.0.5H_2O$: C, 49.5; H, 5.3; N, 8.2 found C, 49.4; H 5.3; N, 7.8%.

EXAMPLE 76 : 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]-2,6-di-tert-butylphenoxyacetic acid.

A solution of methyl 4-(2-[4-(4-pyridyl)piperazin-1-yl]acetyl)-2,6-di-tert-butylphenoxyacetate (241 mg) in dioxane (2.0 ml) was treated with 1N hydrochloric acid and the mixture heated at 100°C for 20 hours. The mixture was cooled, diluted with water, filtered and the filtrate freeze-dried. The solid residue was purified by flash chromatography on silica eluting with toluene/ethyl acetate/0.880 ammonia/ethanol (60:20:10:35 v/v/v/v). The fractions containing the desired product were evaporated, the residue treated with dioxane, filtered and the filtrate diluted with water and freeze dried to give a white foam, which on drying at 55°C gave the title compound, 90 mg: NMR (d_6DMSO) δ 8.16 (2H, d), 7.97 (2H, s), 6.84 (2H, d), 4.22 (2H, s), 3.86 (2H, s), 3.37 (4H, t), 2.64 (4H, t), 1.39 (18H, s); m/e 468 (M+H)$^+$; calculated for $C_{27}H_{37}N_3O_4.2H_2O$: C, 64.4; H, 8.2; N, 8.3. found C, 64.6; H, 7.9; N, 7.9%.
The starting material was prepared as follows:-

(i) In a similar manner to Example 66 step (i), but starting from 2,5-di-tert-butyl-4-hydroxyacetophenone there was obtained from the ethyl acetate extracts a brown oil. Flash chromatography on silica, eluting with successively hexane, then 2% v/v ethyl acetate/hexane and finally 5% v/v ethyl acetate/hexane gave methyl 4-acetyl-2,6-di-tert-butylphenoxyacetate in 50% yield as an oil: NMR (d_6DMSO) δ 7.84 (2H, s), 4.38 (2H, s), 3.76 (3H, s), 2.55 (3H, s), 1.40 (18H, s); m/e 321 (M+H)$^+$; calculated for $C_{19}H_{28}O_4$: C, 71.2; H, 8.8. found C, 71.5; H, 9.0%.
(ii) A mixture of the product from step (i) above (4.91 g) and cupric bromide (6.82 g) in ethyl acetate (45 ml) was heated at reflux temperature for 24 hours. On cooling, the mixture was filtered and the filtrate concentrated in vacuo. The residue on purification by flash chromatography on silica, eluting with 5% v/v ethyl acetate/hexane, gave methyl 4-bromoacetyl-2,6-di-tert-butylphenoxyacetate, 4.98 g, as an oil: NMR (d_6DMSO) δ 7.90 (2H, s), 4.92 (2H, s), 4.40 (2H, s), 3.76 (3H, s), 1.41 (18H, s).
(iii) In a similar manner to Example 5, but starting from the product of step (ii) above and with purification by flash chromatography on silica eluting successively with dichloromethane then 2 to 5% v/v methanol/dichloromethane there was obtained a solid. Trituration with ether gave methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]-2,6-di-tert-butylphenoxyacetate in 33% yield: m.p. 140-142°C; NMR (d_6DMSO) δ 7.97 (2H, s), 6.82 (2H, d), 4.39 (2H, s), 3.85 (2H, s), 3.75 (3H, s), 3.33 (4H, t), 2.64 (4H, t), 1.39 (18H, s); m/e 482 (M+H)$^+$; calculated for $C_{28}H_{39}N_3O_4$: C, 69.8; H, 8.2; N, 8.7. found: C, 69.7; H, 8.6; N, 8.1%.

EXAMPLE 77 : Ethyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]benzoate.

Prepared in a similar manner to Example 5, but starting from ethyl 4-bromoacetylbenzoate; recrystallisation from methanol gave the title compound in 32% yield as pale yellow crystals: m.p. 147-149°C; NMR (d_6DMSO) δ 8.14 (2H, d), 8.08 (4H, q), 6.78 (2H, d), 4.35 (4H, q, AB pattern), 3.98 (2H, s), 3.31 (4H, t), 2.63 (4H, t), 1.35 (3H, t); m/e 354 (M+H)$^+$; calculated for $C_{20}H_{23}N_3O_3$: C, 68.0; H, 6.6; N, 11.9. found: C, 68.0; H, 6.5; N, 11.7%.

EXAMPLE 78 : Sodium 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]benzoate.

A stirred suspension of the product of Example 77 (353 mg) in methanol (5 ml) was treated with a 1 molar sodium hydroxide solution (3 ml). After 2 hours, the cream coloured solid was collected, washed with a little methanol and dried to give the title compound, 240 mg, m.p. >300°C; NMR (d_6DMSO) δ 8.15 (2H, d), 8.05 (4H, t, AB pattern), 6.85 (2H, d), 3.97 (2H, s), 3.38 (4H, t), 2.65 (4H, t), m/e 348 (M+H)$^+$; calculated for $C_{18}H_{18}N_3NaO_3$. $0.25H_2O$: C, 61.4; H, 5.3; N, 11.9. found: C, 61.3; H, 5.2; N, 11.7%.

EXAMPLE 79 : 2-[4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenoxy]isobutyric acid, dihydrobromide.

A mixture of methyl 2-[4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenoxy]isobutyrate (50 mg), 48% w/v hydrobromic acid (0.74 ml), dioxane (1 ml) and water (3 ml) was heated at 95°C for 4 hours. The solution was cooled, diluted with water and freeze-dried to give the title compound, 40 mg, as a pale yellow solid: m.p. 163-167°C; NMR (D_2O) δ 8.40 (2H, d), 8.16 (2H, d), 7.40 (2H, d), 7.21 (2H, d), 5.21 (2H, s), 4.32 (4H, b), 3.89 (4H, bt), 1.86 (6H, s); m/e 384 (M+H)$^+$; calculated for $C_{21}H_{25}N_3.2HBr.2H_2O$: C, 43.3; H, 5.3; N, 7.2. found: C, 43.6; H, 5.3; N, 7.3%.
The starting material was prepared as follows:-

(i) In a similar manner to Example 66 step (ii) but starting from methyl 2-(4-acetylphenoxy)isobutyrate and purification by flash chromatography on silica, eluting with ethyl acetate/hexane (1:2 v/v), there was obtained methyl 2-(4-

bromoacetylphenoxy)isobutyrate in 45% yield as an orange oil: NMR ($CDCl_3$) δ 7.91 (2H, d), 6.85 (2H, d), 4.48 (2H, s), 3.76 (3H, s), 1.67 (6H, s). m/e 315/317 $(M+H)^+$ 2 Br pattern.

(ii) The product from step (i) above (2.00 g) in acetonitrile (10 ml) was added dropwise over 15 minutes to a stirred solution of 1-(4-pyridyl)piperazine (1.04 g) and triethylamine (0.89 ml) in acetonitrile (15 ml) and the mixture stirred overnight. The precipitated solid was removed by filtration and the filtrate evaporated. Purification of the residue by flash chromatography on silica, eluting with 0 to 5% v/v methanol/dichloromethane, gave a yellow gum. Trituration of this gum with diethyl ether gave methyl 2-[4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenoxy]isobutyrate, 170 mg, as a white solid: m.p. 88-90°C; NMR (d_6DMSO) δ 8.15 (2H, d), 7.96 (2H, d), 6.82 (4H, m), 3.92 (2H, s), 3.70 (3H, s), 3.33 (4H, t), 2.63 (4H, t), 1.60 (6H, s); m/e 398 $(M+H)^+$; calculated for $C_{22}H_{27}N_3O_4.0.25H_2O$: C, 65.8; H, 6.8; N, 10.5. found: C, 65.8; H, 7.1; N, 10.4%.

EXAMPLE 80 : Ethyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenoxyacetate.

Ethyl 4-bromoacetylphenoxyacetate (6.0 g) was added to a stirred, cooled (4°C) solution of 1-(4-pyridyl)piperazine (6.5 g) in acetonitrile (225 ml). Stirring was continued for 1 hour at 4°C, then overnight at ambient temperature when the precipitated solid was removed by filtration. The filtrate was evaporated in vacuo and the solid residue triturated with water, filtered, then washed with water and dried. Recrystallisation from a small volume of ethanol gave the title compound, 1.71 g, as a cream coloured solid: m.p. 113-114°C; NMR (d_6DMSO) δ 8.15 (2H, d), 7.98 (2H, d), 7.02 (2H, d), 6.80 (2H, d), 4.89 (2H, d), 4.17 (2H, q), 3.84 (2H, s), 3.32 (4H, t), 2.62 (4H, t), 1.22 (3H, t); m/e 384 $(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4$: C, 65.8; H, 6.6; N, 11.0. found: C, 65.5; H, 6.6; N, 10.8%.
The starting material was prepared as follows:-

(i) In a similar manner to Example 67 step (i), but starting from ethyl bromoacetate there was prepared ethyl 4-acetylphenoxyacetate as a crystalline solid in quantitative yield. The product was used without further purification.

(ii) In a similar manner to Example 76 step (ii), but starting from the product of step (i) above there was prepared ethyl 4-bromoacetylphenoxyacetate in 47% yield as a solid: m.p. 41-42°C; NMR (d_6DMSO) δ 7.90 (2H, d), 7.05 (2H, d), 4.90 (2H, s), 4.72 (2H, s), 4.18 (2H, q), 1.33 (3H, t).

EXAMPLE 81 : iso-Propyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenoxyacetate.

iso-Propyl 4-bromoacetylphenoxyacetate (6.3 g) was added to a stirred, cooled (4°C) solution of 1-(4-pyridyl)piperazine (6.5 g) in acetonitrile (225 ml). Stirring was continued for 1 hour at 4°C, then overnight at ambient temperature when the precipitated solid was removed. The filtrate was evaporated in vacuo and the residue partitioned between ethyl acetate and water. The organic phase was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica, eluting firstly with 0 to 10% v/v methanol/dichloromethane and then toluene/ethyl acetate/.880 ammonium hydroxide/ethanol (60:20:10:35 v/v/v/v), gave a cream solid. Recrystallisation from iso-propanol gave the title compound, 2.1 g: m.p. 121-122°C; NMR (d_6DMSO) δ 8.14 (2H, d), 7.98 (2H, d), 7.02 (2H, d), 6.80 (2H, d), 4.99 (1H, m), 4.85 (2H, s), 3.84 (2H, s), 3.33 (4H, t), 2.62 (4H, t), 1.22 (6H, d); m/e 398 $(M+H)^+$; calculated for $C_{22}H_{27}N_3O_4$: C, 66.5; H, 6.9; N, 10.6. found: C, 65.8; H, 6.8; N, 10.4%.
The starting material was prepared as follows:-

(i) In a similar manner to Example 67 step (i), but starting from iso-propyl bromoacetate there was prepared iso-propyl 4-acetylphenoxyacetate as a crystalline solid in quantitative yield. The product was used without further purification.

(ii) In a manner similar to Example 76 step (ii), but starting from the product of step (i) above and using iso-propyl acetate in place of ethyl acetate as solvent, there was prepared iso-propyl 4-bromoacetylphenoxyacetate as a crystalline solid in 69% yield: m.p. 64-66°C; NMR (d_6DMSO) δ 7.98 (2H, d), 7.06 (2H, d), 4.99 (1H, m), 4.88 (2H, s), 4.83 (2H, s), 1.22 (6H, d).

EXAMPLE 82 : tert-Butyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetylphenoxyacetate.

Prepared in a similar manner to Example 80, but starting from tert-butyl 4-bromoacetylphenoxyacetate. After evaporation of the acetonitrile solution the residue was purified by column chromatography on silica, eluting with 0 to 5% v/v methanol/dichloromethane, to give a yellow oil. Trituration with diethyl ether gave the title compound in 35% yield as a solid: m.p. 103-104°C; NMR (d_6DMSO) δ8.15 (2H, d), 7.98 (2H, d), 7.00 (2H, d), 6.82 (2H, d), 4.76 (2H, s), 3.84 (2H,

s), 3.37 (4H, t), 2.62 (4H, t), 1.43 (9H, s); m/e 412 $(M+H)^+$ calculated for $C_{23}H_{29}N_3O_4$: C, 67.1; H, 7.1; N, 10.2. found: C, 66.9; 7.3; N, 10.0%.
The starting material was prepared as follows:-

(i) In a similar manner to Example 67 step (i), but starting from tert-butyl bromoacetate there was prepared tert-butyl 4-acetylphenoxyacetate as a crystalline solid in 90% yield: m.p. 59-61°C; NMR (d_6DMSO + d_4 acetic acid) δ 7.94 (2H, d), 6.98 (2H, d), 4.21 (2H, s), 2.52 (3H, s), 1.44 (9H, s).

(ii) A solution of the product from step (i) above (3.3 g) and N-bromosuccinimide (2.35 g) in carbon tetrachloride was heated at reflux temperature for 80 hours. After cooling, the precipitate was removed by filtration and the filtrate concentrated in vacuo. Purification of the residual oil by flash chromatography on silica, eluting with 5% v/v ethyl acetate/toluene, gave tert-butyl 4-bromoacetylphenoxyacetate, 1.9 g, as a crystalline solid: m.p. softens at 110-116°C; NMR (d_6DMSO) δ 7.97 (2H, d), 7.04 (2H, d), 4.84 (2H, s), 4.80 (2H, s), 1.43 (9H, s).

EXAMPLE 83 : Neopentyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenoxyacetate.

Prepared in a similar manner to Example 80, but starting from neopentyl 4-bromoacetylphenoxyacetate. After evaporation of the acetonitrile filtrate, the residue was purified by flash chromatography on silica, eluting with 0 to 5% v/v methanol dichloromethane, to give an oil. Trituration with diethyl ether/hexane gave the title compound in 23% yield as a solid: m.p. 88-90°C; NMR (d_6DMSO) δ 8.14 (2H, d), 7.98 (2H, d), 7.04 (2H, d), 6.81 (2H, d), 4.97 (2H, s), 3.83 (4H, s), 3.32 (4H, t), 2.61 (4H, t), 0.86 (9H, s); m/e 426 $(M+H)^+$; calculated for $C_{24}H_{31}N_3O_4$: C, 67.7; H, 7.3; N, 9.9. found: C, 68.1; H, 7.4; N, 9.9%.
The starting material was prepared as follows:-

To a stirred suspension of 4-acetylphenoxyacetic acid (4.36 g) in dichloromethane (50 ml) was added oxalyl chloride (2.36 ml) and DMF (one drop). The mixture was stirred for one hour and then the solvent removed in vacuo to give a yellow oil (4.8 g). A solution of this oil in diethyl ether was added dropwise to a stirred solution of neopentyl alcohol (2.18 g) and triethylamine (3.4 ml) in diethyl ether (50 ml). After the addition, stirring was continued for a further 18 hours when the precipitated solid was removed by filtration. Evaporation of the filtrate and purification of the residue by flash chromatography on silica, eluting with dichloromethane, gave neopentyl 4-acetylphenoxyacetate, 5.1 g, as a pale yellow oil: NMR ($CDCl_3$) δ 7.94 (2H, d), 6.95 (2H, d), 4.72 (2H, s), 3.91 (2H, s), 2.56 (3H, s), 0.93 (9H, s).

(ii) To a stirred solution of the product of step (i) above (2.64 g) in chloroform (25 ml), was added slowly over 10 minutes, a solution of bromine (0.52 ml) in chloroform (10 ml). Stirring was continued for a further hour and the solvent removed in vacuo. Trituration of the residue with diethyl ether/hexane gave neopentyl 4-bromoacetylphenoxyacetate, 2.3 g, as a crystalline solid: m.p. 85-87°C.

EXAMPLE 84 : Dimethyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenoxymalonate.

Prepared in a similar manner to Example 80, but starting from dimethyl 4-bromoacetylphenoxymalonate and after evaporation of the aceconitrile filtrate the residue was partitioned between water/dichloromethane. The organic solution was dried ($MgSO_4$), concentrated and purification by flash chromatography, eluting with 0 to 5% v/v methanol/dichloromethane, then trituration with diethyl ether gave the title compound in 31% yield as a pale yellow solid: m.p. 115-116°C; NMR (d_6DMSO) δ 8.16 (2H, d), 8.02 (2H, d), 7.09 (2H, d), 6.82 (2H, d), 5.95 (1H, s), 3.86 (2H, s), 3.80 (6H, s), 3.34 (4H, t), 2.63 (4H, t); m/e 428 $(M+H)^+$; calculated for $C_{22}H_{25}N_3O_6$: C, 61.8; H, 5.9; N, 9.8. found C, 61.3; H, 5.9; N, 9.2%.
The starting material was prepared as follows:-

(i) In a similar manner to Example 67 step (i), but starting from dimethyl bromomalonate and purification by flash chromatography on silica, eluting with 50 to 75% v/v diethyl ether/hexane, there was prepared dimethyl 4-acetylphenoxymalonate in 53% yield as a white crystalline solid: m.p. 71-72°C; NMR (d_6DMSO) δ 7.95 (2H, d), 7.09 (2H, d), 5.95 (1H, s), 3.78 (6H, s), 2.53 (3H, s); m/e 267 $(M+H)^+$; calculated for $C_{13}H_{14}O_6$: C, 58.6; H, 5.3. found: C, 58.9; H, 5.3%.

(ii) In a similar manner to Example 76 step (ii), but starting from the product of step (i) above and using methyl acetate in place of ethyl acetate as solvent, there was prepared methyl 4-bromoacetylphenoxymalonate in 59% yield as a white crystalline solid: m.p. 114-115°C; NMR (d_6DMSO) δ 7.99 (2H, d), 7.12 (2H, d), 5.99 (1H, s), 4.86 (2H, s), 3.80 (6H, s).

EXAMPLE 85 : 4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenoxyacetamide.

A solution of the product of Example 1 (200 mg) in methanol (10 ml), prepared under argon, was cooled to 4°C and saturated with dry ammonia gas, then sealed in a pressure bottle and kept for 2 days. The orange crystals which formed, after filtration and washing with a little methanol, gave the title compound, 140 mg: m.p. 247 to 248°C; NMR (d_6DMSO) δ 8.16 (2H, d), 7.99 (2H, d), 7.55 (1H, bs), 7.37 (1H, bs), 7.02 (2H, d), 6.81 (2H, d), 4.54 (2H, s), 3.85 (2H, s), 3.33 (4H, t), 2.60 (4H, t); m/e 355 $(M+H)^+$; calculated for $C_{19}H_{22}N_4O_3$: C, 64.4; H, 6.3; N, 15.8. found: C, 64.4; H, 6.4; N, 15.6%.

EXAMPLE 86 : 2-[4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenoxy]-N-methylacetamide.

A suspension of the product of Example 1 (100 mg) in a 33% w/v solution of methylamine in ethanol (3 ml) was stirred for 18 hours. The solid formed, after filtration and washing with a little ethyl acetate, gave the title compound, 65 mg: m.p. 169-171°C; NMR (d_6DMSO) δ 8.14 (2H, d), 8.06 (1H, bq), 8.00 (2H, d), 7.05 (2H, d), 6.80 (2H, d), 4.56 (2H, s), 3.82 (2H, s), 3.30 (4H, t), 2.66 (3H, d), 2.61 (4H, t); m/e 369 $(M+H)^+$; calculated for $C_{20}H_{24}N_4O_3$: C, 65.2; H, 6.6; N, 15.2. found: C, 65.0; H, 6.8; N, 15.1%.

EXAMPLE 87 : 2-[4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenoxy]-N-(2-methoxyethyl) acetamide.

A suspension of the product of Example 1, (100 mg) in 2-methoxyethylamine (1 ml) was stirred for 18 hours. Filtration of the solid and washing with ethyl acetate gave the title compound, 70 mg, as a white crystalline solid: m.p. 142-145°C; NMR (d_6DMSO + d_4 acetic acid) δ 8.20 (2H, d), 8.00 (2H, d), 7.14 (2H, d), 7.06 (2H, d), 4.62 (2H, s), 3.72 (4H, t), 3.38 (4H, m), 3.26 (3H, s), 2.78 (4H, t); m/e 413 $(M+H)^+$; calculated for $C_{22}H_{28}N_4O_4$: C, 64.1; H, 6.8; N, 13.6. found: C, 63.9; H, 6.8; N, 13.3%.

EXAMPLE 88 : 2-[4-[2-[4-(4-Pyridyl)piperazin-1-yl]acetyl]phenoxy]-N-(phenylmethyl)acetamide.

A solution of 2-[4-(bromoacetyl)phenoxy]-N-(phenylmethyl)acetamide (1.40 g) (preparation described in EPO 052442) in acetonitrile (5 ml) was added to a stirred solution of 1-(4-pyridyl)piperazine (1.14 g) in acetonitrile (20 ml). After stirring overnight the liquors were decanted from the residual gum, then concentrated in vacuo. Purification by flash chromatography on silica, eluting with 2 to 5% v/v methanol/dichloromethane, gave a solid. Trituration of this solid with diethyl ether gave the title compound, 95 mg: m.p. 150-151°C; NMR (d_6DMSO) δ 8.67 (1H, bt), 8.15 (2H, d), 8.00 (2H, d), 7.26 (5H, m), 7.06 (2H, d), 6.81 (2H, d), 4.66 (2H, s), 4.34 (2H, d), 3.84 (2H, s), 3.33 (4H, t), 2.54 (4H, t); m/e 445 $(M+H)^+$; calculated for $C_{26}H_{28}N_4O_3$. $0.25H_2O$: C, 69.5; H, 6.4; 12.5. found: C, 69.6; H, 6.4; N, 12.3%.

EXAMPLE 89 : Methyl N-[4-[2-[4-(4-pyridyl)piperazin-1-yl]acetyl]phenoxyacetyl]glycinate.

A solution of methyl N-[4-(bromoacetyl)phenoxyacetyl]glycinate (0.85 g) in acetonitrile (10 ml) was added to a stirred solution of 1-(4-pyridyl)piperazine (0.81 g) in acetonitrile (30 ml). After stirring overnight the solvent was removed in vacuo and the residue partitioned between water/ethyl acetate. The organic phase was washed with water, then dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica, eluting with 0 to 7.5% v/v methanol/dichloromethane. Evaporation of the fractions gave the title compound, 130 mg, as a foam: NMR (d_6DMSO) δ 8.58 (1H, t), 8.16 (2H, d), 8.01 (2H, d), 7.08 (2H, d), 6.83 (2H, d), 5.75 (1H, s), 4.68 (2H, s), 3.92 (2H, d), 3.84 (2H, s), 3.65 (3H, s), 3.34 (4H, t+H_2O), 2.65 (4H, t); m/e 427 $(M+H)^+$; calculated for $C_{22}H_{26}N_4O_5$. $0.5CH_2Cl_2$: C, 57.6; H, 5.8; N, 11.9. found: C, 57.8; H, 5.7; N, 12.0%.
The starting material was prepared as follows:-

(i) To a stirred suspension of 4-(acetyl)phenoxyacetic acid (3.00 g) in dichloroaethane (40 ml) was added oxalyl chloride (1.62 ml) and 1 drop of DMF. Stirring was continued for 1.5 hours and the clear solution on evaporation gave an oil (I). Triethylamine (4.30 ml) was added slowly to a stirred, cooled (4°C) suspension of methyl glycinate hydrochloride (1.95 g) in dichloromethane (25 ml) under argon. After stirring for 10 minutes, a solution of (I) in dichloromethane (10 ml) was added and stirring continued for a further 2 hours. The precipitate was removed by filtration and the filtrate concentrated in vacuo. Purification of the residue by flash chromatography on silica, eluting with 2% v/v methanol/dichloromethane, gave a solid. Trituration with ether/hexane gave ethyl N-[4-(acetyl)phenoxyacetyl]glycinate, 3.1 g, as white crystals: m.p. 120-121°C; NMR (d_6DMSO) δ 8.57 (1H, t), 7.94 (2H, d), 7.07 (2H, d), 4.66 (2H, s), 3.92 (2H, s), 3.64 (3H, s), 2.52 (3H, s); m/e 266 $(M+H)^+$; calculated for $C_{13}H_{15}NO_5$: C, 58.9; H, 5.7; N, 5.3. found: C, 58.4; H, 5.5; N, 5.0%.

(ii) The product of step (i) (3.00 g) and N-bromosuccinimide (2.02 g) in carbon tetrachloride (50 ml) was heated at reflux temperature for 64 hours. The solvent was evaporated and the black residue dissolved in methanol/ethyl acetate, treated with charcoal, filtered and then evaporated. The resulting brown oil was purified by flash chromatography on silica, eluting with dichloromethane. Trituration with hexane gave methyl N-[4-(bromoacetyl)phenoxyacetyl]glycinate, 0.85 g, as a solid: mp softens 109-111°C; NMR (d_6DMSO) δ 8.60 (1H, bt), 7.99 (2H, d), 7.09 (2H, d), 4.84 (2H, s), 4.69 (2H, s), 3.91 (2H, d), 3.64 (3H, s).

EXAMPLE 90 : Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]ethyl]phenoxyacetate.

A mixture of methyl 4-[1-(2-methanesulphonyloxyethyl)]phenoxyacetate (2.0 g) and 1-(4-pyridyl)piperazine (2.26 g) in acetonitrile was heated at reflux temperature for 25 hours. The solvent was removed in vacuo and the residue purified by flash chromatography on silica, eluting with successively 2.5, 3, 3.5, and 4% v/v methanol/dichloromethane. Isolation of the desired fractions and trituration with diethyl ether gave the title compound, 600 mg: recrystallisation from methanol gave white crystals, m.p. 104-105°C; NMR (d_6DMSO) δ 8.15 (2H, d), 7.15 (2H, d), 6.86 (2H, d), 6.82 (2H, d), 4.74 (2H, s), 3.69 (3H, s), 3.30 (4H, t. 2H, m. + H_2O), 2.71 (2H, m), 2.54 (4H, t), m/e 356 $(M+H)^+$, calculated for $C_{20}H_{25}N_3O_3$. $0.25H_2O$: C, 66.7; H, 7.1; N, 11.7. found: C, 67.0; H, 7.2; N, 11.4%.
The starting material was prepared as follows:-

(i) A mixture of 4-hydroxyphenethyl alcohol (5.37 g), anhydrous potassium carbonate (5.37 g) and methyl bromoacetate (3.80 ml) in anhydrous acetone (50 ml) was stirred for 18 hours. The mixture, after filtration, was evaporated and the residue after purification by flash chromatography on silica, eluting with 2% v/v methanol/dichloromethane, gave methyl 4-[1-(2-hydroxyethyl)]phenoxyacetate, 5.05 g, as an oil: NMR ($CDCl_3$) δ 7.15 (2H, d), 6.86 (2H, d), 4.62 (2H, s), 3.84 (2H, m), 3.80 (3H, s), 2.81 (2H, t), 1.40 (1H, bt); m/e 210 $(M)^+$; calculated for $C_{11}H_{14}O_4$: C, 62.8; H, 6.7. found: C, 62.8; H, 6.8%

(ii) Methanesulphonyl chloride (0.98 ml) was added dropwise, over 30 minutes, to a stirred, cooled (4°C) solution of the product from step (i) (2.22 g) and triethylamine (1.91 ml) in dichloromethane (35 ml) under argon. After 2 hours, the solvent was evaporated and the residue partitioned between ethyl acetate (75 ml) and water (20 ml). The organic phase was separated, washed with saturated sodium chloride solution (3x15 ml), dried and evaporated. The residue on purification by flash chromatography on silica, eluting with 45% v/v ethyl acetate/hexane, gave methyl 4-[1-(2-methanesulphonyloxyethyl)]phenoxyacetate, 2.85 g, as an oil: NMR ($CDCl_3$) δ 7.16 (2H, d), 6.87 (2H, d), 4.62 (2H, s), 4.38 (2H, t), 3.81 (3H, s), 3.00 (2H, t), 2.85 (3H, s); m/e 288 (M^+); calculated for $C_{12}H_{16}O_6S$: C, 50.0; H, 5.6; S, 11.1. found: C, 50.1; H, 5.5; S, 11.0%.

EXAMPLE 91 : 4-[2-[4-(4-pyridyl)piperazin-1-yl]ethyl]phenoxyacetic acid dihydrochloride.

In a similar manner to Example 71, but starting from the product of Example 90, there was obtained the title compound in 95% yield: m.p. 270-273°C; NMR (d_6DMSO + d_4 acetic acid) δ 8.34 (2H, d), 7.30 (2H, d), 7.22 (2H, d), 6.91 (2H, d), 4.67 (2H, s), 4.06 (4H, b), 3.46 (4H, b), 3.35 (2H, m), 3.05 (2H, m); m/e 342 $(M+H)^+$; calculated for $C_{19}H_{22}N_3O_3.2HCl$: C, 55.0; H, 6.5; N, 10.1. found: C, 54.8; H, 6.2; N, 9.8%.

EXAMPLE 92 : Tertiary butyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]carbonylmethyl]phenoxyacetate.

In a similar manner to Example 18 step (iv), but starting from tertiary butyl 4-(carboxymethyl)phenoxyacetate, there was obtained after flash chromatography on silica, eluting with 0 to 5% v/v methanol/dichloromethane, a gum. Further purification by flash chromatography on neutral alumina, eluting with 1% v/v methanol/dichloromethane followed by trituration with diethyl ether gave the title compound in 17% yield as a white solid: m.p. 110-112°C; NMR (d_6DMSO) δ 8.22(2H, d), 7.15(2H, d), 7.06(2H, d), 6.83(2H, d), 4.60(2H, s), 3.70(2H, s), 3.62(4H, bt), 3.38(4H, bt + H_2O), 1.42(9H, s); m/e 412 $(M+H)^+$; calculated for $C_{23}H_{29}N_3O_4.0.25H_2O$: C, 66.4; H, 7.1; N, 10.1. found: C, 66.4; H, 7.2; N, 10.1%.
The starting material was prepared as follows:-

(i) Sodium hydride (50% w/w dispersion in mineral oil, 3.7g) was treated under argon with repeated washes of hexane. The oil-free residue was suspended in dry DMF (100 ml) and 4-hydroxyphenylacetic acid (13.0g) was added portionwise to the stirred cooled (4°C) mixture. After 30 minutes, benzyl bromide (9.2ml) was added dropwise and, after a further 1 hour at 4°C, stirring was continued overnight at ambient temperature. The solvent was evaporated in vacuo and the residue partitioned between ethyl acetate and water. The aqueous phase was re-extracted with further ethyl acetate and the combined organic extracts washed with water and brine, then dried ($MgSO_4$) and evaporated. The crystalline residue gave benzyl 4-hydroxyphenylacetate, 17.8g, as off-white crystals: m.p. 70-

72°C; NMR ($CDCl_3$) δ 7.32(5H, m), 7.14(2H, d), 6.76(2H, d), 5.12(2H, s), 3.59(2H, s); m/e 242 $(M^{\cdot})^+$.

(ii) Sodium hydride (50% w/w dispersion in mineral oil, 2.1g) was treated under argon with repeated washes of hexane. The oil-free residue was suspended in dry DMF (130 ml) and the product from step (i) (10g) added in three portions to the cooled (4°C) stirred mixture. Stirring was continued for a further 15 minutes when tertiary butyl bromoacetate (7.0 ml) was added dropwise over 15 minutes. After 1 hour at 4°C, the mixture was stirred for 6 hours at ambient temperature. The solvent was evaporated in vacuo and the residue partitioned between ethyl acetate and water. The aqueous phase was re-extracted with further ethyl acetate and the combined organic phases washed with water and brine, then dried ($MgSO_4$) and evaporated. The residue, after purification by flash chromatography on silica eluting with dichloromethane, gave tertiary butyl 4-(benzyloxycarbonylmethyl)phenoxyacetate, 7.5g, as a colourless oil: NMR ($CDCl_3$) d 7.31(5H, m), 7.20(2H, m), 6.85(2H, m), 5.12(2H, s), 4.49(2H, s), 3.60(2H, s), 1.48(9H, s); m/e 356 $(M^{\cdot})^+$.

(iii) In a similar manner to Example 18 step (iii) but starting from the product of step (ii) above was prepared tertiary butyl 4-(carboxymethyl)phenoxyacetate in 96% yield as a white crystalline solid: m.p.78-80°C; NMR (d_6DMSO) δ 7.15(2H, d), 6.82(2H, d), 4.60(2H, s), 3.48(2H, s), 1.43(9H, s); m/e 266 $(M^{\cdot})^+$; calculated for $C_{14}H_{18}O_5.0.75H_2O$: C, 60.1; H, 7.0. found: C, 59.9; H, 7.2%.

EXAMPLE 93 : 4-[2-[4-(4-pyridyl)piperazin-1-yl]carbonylmethyl]phenoxyacetic acid, dihydrochloride.

A solution of the product from Example 92 (50 mg) in a mixture of dioxane (1 ml), water (2 ml) and 1 molar hydrochloric acid solution (0.61 ml) was heated overnight at 90°C. The resulting solution, on dilution with water and freeze-drying, gave the title compound, 30mg, as a yellow foam: NMR (d_6DMSO + d^4 acetic acid) δ 8.31(2H, d), 7.24(2H, d), 7.18(2H, m), 6.87(2H, m), 4.64(2H, s), 3.96(4H, t), 3.72(2H, s), 3.32(4H, t); m/e 356 $(M+H)^+$; calculated for $C_{19}H_{21}N_3O_4.2HCl.2.5H_2O$: C, 48.2; H, 5.9; N, 8.9. found C, 48.5; H, 6.0; N, 8.8%.

EXAMPLE 94 : Methyl 4-[2-[4-(2-methylpyrid-4-yl)piperazin-1-yl]acetyl]phenoxyacetate

Methyl 4-bromoacetylphenoxyacetate (1.72g) was added to a stirred mixture of 1-[4-(2-methylpyridyl)]piperazine dihydrochloride (1.5g) and triethylamine (2.5 ml) in acetonitrite (25 ml). Stirring was continued overnight when the solvent was removed in vacuo. Purification by flash chromatography, first on silica eluting with 10% v/v methanol/dichloromethane and then on neutral alumina eluting with 1% v/v methanol/dichloromethane, gave the title compound, 418 mg, as a white solid: m.p. 155-157°C; NMR (d_6DMSO) δ 8.00(3H, m), 7.04(2H, d), 6.70(1H, d), 6.64(1H, dd), 4.92(2H, s), 3.83(2H, s), 3.71(3H, s), 3.30(4H, b+ H_2O), 2.61(4H, t), 2.32(3H, s); m/e 384 $(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4$: C, 65.8; H, 6.6; N, 11.0. found: C, 65.4; H, 6.8; N, 10.9%.
The starting material was prepared as follows:-

(i) A mixture of 4-chloro-2-picoline (5 g) and 1-benzylpiperazine (13.6 ml) in xylene (50 ml) was heated at reflux temperature for 18 hours. The solution was cooled and the solid precipitate removed by filtration and the filtrate concentrated in vacuo. Purification by flash chromatography on silica, eluting with 20% v/v methanol/dichloromethane gave 4-[4-(2-picolyl)]-1-benzylpiperazine, 9.54g, as a light fawn crystalline solid: m.p. 94-95°C; NMR ($CDCl_3$) δ 8.15(1H, d), 7.30(5H, m), 6.51(2H, m), 3.57(2H, s), 3.44(4H, t), 2.57(4H, t), 2.46(3H, s); m/e 168 $(M+H)^+$; calculated for $C_{17}H_{21}N_3$: C, 76.4; H, 7.9; N, 15.7. found: C, 75.7; H, 8.1; N, 15.7%.

(ii) 10% w/w Palladium on charcoal (1.5 g) was added to a stirred solution of the product of step (i) (9.00g) and 2 molar hydrochloric acid (34 ml) in methanol (180 ml) and the mixture was hydrogenated at room temperature and pressure until the theoretical amount of hydrogen had been taken up. Charcoal was added, the mixture stirred for 5 minutes then filtered through diatomaceous earth and the filtrate on evaporation to dryness gave 1-[4-(2-methylpyridyl)]piperazine dihydrochloride, 10.6 g, as a fawn solid: m.p. 64-68°C; NMR (d_6DMSO) δ 8.20(1H, d), 7.18(1H, d), 7.12(1H, dd), 3.92(4H, t), 3.19(4H, t), 2.51(3H, s + DMSO); m/e 178 $(M+H)^+$; calculated for $C_{10}H_{15}N_3.2HCl.0.75H_2O$: C, 45.5; H, 7.0; N, 15.9. found: C, 45.3; H, 7.0; N, 15.8%.

EXAMPLE 95 : 4-[2-[4-(2-methylpyrid-4-yl)piperazin-1-yl]acetyl]phenoxyacetic acid, dihydrobromide.

A mixture of the product of Example 94 (160 mg), 48% w/v hydrobromic acid (0.25 ml) and dioxane (1 ml) in water (3 ml) were heated at 90°C for 30 minutes. The solution was cooled, further water added and the mixture freeze-dried. Trituration of the residue with absolute ethanol gave the title compound, 50 mg, as a fawn solid: m.p. 146-148°C; NMR (d_6DMSO + d_4 acetic acid) δ 8.17(1H, d), 7.95(2H, d), 7.09(4H, m), 4.94(2H, s), 4.78(2H, s), 3.99(4H, b), 3.07(1H, q), 2.46(3H, s), 1.17(1.5H, t); m/e 370 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4.2HBr.H_2O.0.5C_2H_5OH$: C, 44.1; H, 5.3; N, 7.3. found: C, 44.0; H, 5.4; N, 7.2%.

EXAMPLE 96 : Methyl 4-[1-(4-pyridyl)piperidin-4-yl]oxyphenoxyacetate

Diethylazodicarboxylate (0.47 ml) was added dropwise over 30 minutes to a stirred mixture of 1-(4-pyridyl)-4-piperidinol (534 mg), methyl 4-hydroxyphenoxyacetate (546 mg), triphenylphosphine (787 mg) and dry THF (30 ml) in an atmosphere of argon and cooled to 4°C. After 1 hour at 4°C, the mixture was allowed to reach ambient temperature and stirred for 48 hours. The solvent was removed by evaporation and the residue purified by flash chromatography on silica eluting with 5% v/v methanol/dichloromethane. Recrystallisation from ethyl acetate/hexane gave the title compound, 532 mg, as a white solid: m.p. 74-76°C; NMR (d_6DMSO) δ 8.15(2H, bd), 6.89(6H, m), 4.71(2H, s), 4.50(1H, m), 3.70(2H, m), 3.69(3H, s), 3.23(2H, m), 1.96(2H, m), 1.62(2H, m); m/e 343 $(M+H)^+$; calculated for $C_{19}H_{22}N_2O_4$: C, 66.7; H, 6.5; N, 8.2. found: C, 66.2; H, 6.7; N, 8.2%.

EXAMPLE 97 : 4-[1-(4-pyridyl)piperidin-4-yl]oxyphenoxyacetic acid

Following the method of Example 2; but starting from the product of Example 96, the title compound was prepared in 85% yield: m.p. 288-291°C; NMR (NaOD + d_6 DMSO) δ 7.97(2H, d), 6.77(4H, m), 6.69(2H, d), 4.35(1H, m), 4.19(2H, s), 3.53(2H, m), 3.08(2H, m), 1.82(2H, m), 1.49(2H, m); m/e 329 $(M+H)^+$; calculated for $C_{18}H_{20}N_2O_4$: C, 65.8; H, 6.1; N, 8.5. found: C, 65.7; H, 6.3; N, 8.4%.

EXAMPLE 98 : Methyl 4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenoxyacetate

Following the method of Example 96, but starting from 4-(4-hydroxymethylpiperidin-1-yl)pyridine, the title compound was prepared in 18% yield: m.p. 127-129°C; NMR (d_6DMSO) δ 8.12(2H, d), 6.84(4H, s), 6.81(2H, d), 4.70(2H, s), 3.96(2H, bd), 3.79(2H, d), 3.70(3H, s), 2.88(2H, dt), 2.01(1H, m), 1.82(2H, bd), 1.30(2H, m), m/e 357 $(M+H)^+$; calculated for $C_{20}H_{24}N_2O_4.0.5H_2O$: C, 65.7; H, 6.9; N, 7.7. found: C, 66.1; H, 6.9; N, 7.8%.

EXAMPLE 99: 4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenoxyacetic acid.

Following the method of Example 2 but starting from the product of Example 98, the title compound was prepared in 86% yield: m.p. 278-281°C; NMR (d_6 DMSO + TFA) δ 8.09(2H, t), 7.08(2H, d), 6.78(4H, s), 4.50(2H, s), 4.20(2H, bd), 3.74(2H, d), 3.17(2H, bt), 2.12(1H, m), 1.91(2H, dm), 1.32(2H, m); m/e 343 $(M+H)^+$; calculated for $C_{19}H_{22}N_2O_4.0.25H_2O$: C, 65.8; H, 6.5; N, 8.1. found: C, 66.0; H, 6.6; N, 8.0%.

EXAMPLE 100 : Methyl 4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenoxyacetate

Following the method of Example 96, but starting from 4-(4-hydroxyethylpiperidin-1-yl)pyridine, the title compound was prepared in 65% yield: m.p. 86-88°C; NMR (d_6DMSO) δ 8.11(2H, d), 6.85(4H, s), 6.79(2H, d), 4.70(2H, s), 3.96(2H, t), 3.92(2H, bd), 3.69(3H, s), 2.81(2H, dt), 1.78(2H, bd), 1.73(1H, m), 1.65(2H, q), 1.20(2H, m); m/e 371 $(M+H)^+$; calculated for $C_{21}H_{26}N_2O_4$: C, 68.1; H, 7.1; N, 7.6. found: C, 67.5; H, 7.3; N, 7.5%.

EXAMPLE 101 : 4-[2-[1-(4-pyridyl)piperidin-4-yl]ethoxy]phenoxyacetic acid

Following the method of Example 2, but starting from the product of Example 100, the title compound was prepared in 74% yield: m.p. 247-249°C; NMR (d_6 DMSO + TFA) δ 8.19(2H, t), 7.19(2H, d), 6.38(4H, s), 4.60(2H, s), 4.25(2H, bd), 4.01(2H, t), 3.20(2H, dt), 1.93(3H, m), 1.70(2H, q), 1.28(2H, m); m/e 357 $(M+H)^+$; calculated for $C_{20}H_{24}N_2O_4$: C, 67.4; H, 6.8; N, 7.9. found: C, 67.0; H, 6.8; N, 7.7%.

EXAMPLE 102 : Methyl 3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]propionate

Following the method of Example 96, but starting from 4-(4-hydroxymethylpiperidin-1-yl)pyridine and methyl 3-(4-hydroxyphenyl)propionate, the title compound was prepared in 14% yield:
m.p. 96.5-98.5°C; NMR (d_6DMSO) δ 8.13(2H, d), 7.11(2H, d), 6.83(4H, m), 3.97(2H, dm), 3.81(2H, d), 3.56(3H, s), 2.87(2H, dt), 2.77(2H, t), 2.57(2H, t), 2.01(1H, m), 1.84(2H, m), 1.30(2H, m); m/e 355 $(M+H)^+$; calculated for $C_{21}H_{26}N_2O_3.0.75H_2O$: C, 68.5; H, 7.2; N, 7.8. found: C, 68.5; H, 7.5; N, 7.6%.

EXAMPLE 103 : 3-[4-[1-(4-pyridyl)piperidin-4-yl]methoxyphenyl]propionic acid

Following the method of Example 2, but starting from the product of Example 161, the title compound was prepared in 80% yield: m.p. 303-307°C; NMR (d_6 DMSO + TFA) δ 8.20(2H, d), 7.25(6H, m), 4.31(2H, dm), 3.88(2H, d), 3.27(2H, bt), 2.82(2H, t), 2.52(2H, t), 2.25(1H, m), 2.00(2H, bd), 1.40(2H, m); m/e 341 $(M+H)^+$; calculated for $C_{20}H_{24}N_2O_3.0.25H_2O$: C, 69.6; H, 7.2; N, 8.1. found: C, 69.6; H, 7.2; N, 8.0%.

EXAMPLE 104 : Methyl 4-[[1-(4-pyridyl)piperidin-4-yl]carboxamido]phenoxyacetate, hydrochloride

Thionyl chloride (5 ml) was added dropwise over ten minutes to a stirred suspension of 1-(4-pyridyl)-4-piperidinecarboxylic acid (2.06 g) in dry dichloromethane (20 ml) at 4°C. After 1 hour at 4°C, the mixture was allowed to reach ambient temperature and stirred for 16 hours. The solvent was removed by evaporation and the residue dried under high vacuum to give a solid foam (2.84 g).

Triethylamine (0.70 ml) was added to a stirred suspension of methyl 4-aminophenoxyacetate hydrochloride (544 mg) in dry dichloromethane (10 ml). After stirring for 1 hour, the mixture was cooled to 4°C, and the foam (0.71 g) added. After 1 hour at 4°C the mixture was allowed to reach ambient temperature and stirred for 16 hours. The precipitated solid was collected, washed with dichloromethane and, on recrystallisation from water, gave the title compound, 744 mg: m.p. 233-234.5°C; NMR (d_6DMSO) δ 13.56(1H, b), 9.98(1H, s), 8.21(2H, d), 7.51(2H, d), 7.20(2H, d), 6.85(2H, d), 4.72(2H, s), 4.25(2H, bd), 3.69(3H, s), 3.27(2H + H_2O), 2.78(1H, m), 1.97(2H, m), 1.67(2H, m); m/e 370 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4.HCl$: C, 59.2; H, 6.0; N, 10.4. found: C, 58.8; H, 6.1; N, 10.3%.

EXAMPLE 105 : 4-4-[[1-([1-(4-pyridyl)piperidin-4-yl]carboxamido]phenoxyacetic acid

Following the method of Example 2, but starting from the product of Example 104, the title compound was prepared in 69% yield: m.p. 285-287°C; NMR(NaOD) δ 8.30(2H,d), 7.44(2H,d), 7.07(2H,d), 7.04(2H,d), 4.60(2H,s), 4.14(2H,bd), 3.11(2H,dt), 2.81(1H,m), 2.11(2H,bd), 1.88(2H,dq); m/e 356$(M+H)^+$; calculated for $C_{19}H_{21}N_3O_4$. H_2O: C, 61.1; H, 6.2; N, 11.3. found: C, 60.9; H, 6.2; N, 11.0%.

EXAMPLE 106 : Methyl 4-[2-[(1-(4-pyridyl)piperidin-4-yl]acetamido]phenoxyacetate.

To a stirred solution of 1-(4-pyridylpiperidin-4-yl)acetic acid hydrochloride (400mg) in dry DMF (5ml) was added N,N'-diisopropylethylamine (1.1ml), HOBT (240mg), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (600mg). After 15 minutes methyl 4-aminophenoxyacetate (280mg) was added and stirring continued overnight. The reaction mixture was added to ethyl acetate (100ml) and this mixture washed with water, 10% w/v sodium hydrogen sulphate solution and brine, then dried ($MgSO_4$) and evaporated. Purification of the resulting gum by flash chromatography, first on silica eluting with 0 to 5% v/v methanol/dichloromethane and then on neutral alumina eluting with 2% v/v methanol/dichloromethane gave, on trituration with diethyl ether the title compound, 55mg, as an off-white solid: m.p. 155-157°C; NMR(d_6DMSO) δ 9.74(1H,s), 8.11(2H,d), 7.48(2H,d), 6.86(2H,d), 6.79(2H,d), 4.73(2H,s), 3.91(2H,bd), 3.70(3H,s), 2.84(2H,dt), 2.21(2H,d), 2.03(1H,m), 1.72(2H,bd), 1.22(2H,dq); m/e 384$(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4$. 0.5 H_2O: C, 64.5; H, 6.6; N, 10.7. found: C, 64.7; H, 6.8; N, 10.8%.

The starting material was prepared as follows:-

(i) A stirred suspension of sodium hydride (50% dispersion in mineral oil, 4.8g, 0.1Moles) in dimethoxyethane (300ml) was ice-cooled and treated under an atmosphere of argon with triethyl phosphonoacetate (19.82ml, 0.1Moles), added dropwise. Stirring was continued for 1 hour during which time the temperature of the mixture was maintained <5 °C. The cooling bath was removed and N-benzylpiperidone (17.85ml, 0.1Moles) was added dropwise. The mixture was stirred overnight at room temperature, then diluted with water (500ml) and extracted with ether (3 X 200ml). The combined organic extracts were washed with water (200ml) and saturated brine (100ml), dried (MgSO4) and concentrated under reduced pressure. The residue was purified by chromatography (flash column, eluted with hexane/ethyl acetate; 3:2) to give ethyl 4-carboxymethylene-N-benzylpiperidine ester (5.52g) as a yellow oil; NMR ($CDCl_3$): 1.1 (t,3H), 2.2 (t,2H), 2.4 (m,4H), 3.4 (s,2H), 4.0 (q,2H), 5.6 (s,1H), 7.2 (m,5H); m/e 260 $(M+H)^+$.

(ii) A solution of ethyl 4-carboxymethylene-N-benzylpiperidine ester (5.5g, 21 mMoles) in ethanol (250ml)was stirred with 10% palladium on carbon under an atmosphere of hydrogen until a total of 950ml of hydrogen had been consumed. An additional quantity of 10% palladium on carbon (500mg) was added and stirring was continued for 4 hours to remove residual starting material. The mixture was filtered and concentrated under reduced pressure to give ethyl 4-carboxymethylpiperidine ester (3.31g) as a slightly green oil which was used without further purification; NMR ($CDCl_3$): 1.0-1.2 (m,2H), 1.25 (t,3H), 1.7 (s,2H), 1.9 (m,1H), 2.2 (d,2H), 2.6 (td,2H), 3.05 (dt,2H), 4.0

(q,2H); m/e 172 $(M+H)^+$.

(iii) A mixture of ethyl 4-carboxymethylpiperidine (3.25g), triethylamine (5.28ml), 4-chloropyridine hydrochloride (2.85g) and xylene (100ml) was heated at reflux temperature overnight. The mixture was cooled, the precipitate removed by filtration and the filtrate evaporated. A solution of the residue in dichloromethane was washed with water, then dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica, eluting with 10% v/v methanol/dichloromethane, gave ethyl 1-(4-pyridylpiperidin-4-yl)acetate, 2.15g, as an oil: NMR($CDCl_3$) δ 8.23(2H,d), 6.64(2H,d), 4.26(2H,q), 3.88(2H,dm), 2.89(2H,dt), 2.27(2H,d), 2.05(1H,m), 1.83(2H,dm), 1.36(2H,dq), 1.27(3H,t); m/e 249$(M+H)^+$.

(iv) A mixture of the product from step (iii) (2.20g), 1 molar hydrochloric acid (35.5ml) and dioxane (100ml) was heated at 95°C for 3 hours. The resulting solution, on freeze-drying, gave 1-(4-pyridylpiperidin-4-yl)acetic acid hydrochloride, 2.3g, as a light-brown powder: m.p. 105-108°C; NMR(d_6DMSO) δ 13.57(1H,b), 8.18(2H,d), 7.17(2H,d), 4.21(2H,bd), 3.17(2H,dt), 2.21(2H,d), 2.09(1H,m), 1.83(2H,dm); 1.22(2H,dq); m/e 221$(M+H)^+$; calculated for $C_{12}H_{16}N_2O_2$. HCl. 1.25 H_2O: C, 51.6; H, 7.0; N, 10.0; Cl,12.7. found C, 51.7; H, 7.0; N, 9.8; Cl,12.2%.

EXAMPLE 107: 4-[2-[1-(4-pyridyl)piperidin-4-yl]acetamido]phenoxyacetic acid dihydrochloride

A mixture of the product from Example 106 (30mg), 1 molar hydrochloric acid (0.40ml), water (2ml) and dioxane (1ml) was heated at 95°C for 1 hour. The resulting solution, on freeze-drying and trituration of the residue with ether, gave the title compound, 25mg, as a light brown solid: m.p. 158-162°C; NMR(d^6DMSO + d^4 acetic acid) 8.17(2H,d), 7.49(2H,d), 7.20(2H,d), 6.85(2H,d), 4.61(2H,s), 4.23(2H,bd), 3.21(2H,bt), 2.21(3H,m); 1.86(2H,bd + acetic acid), 1.28(2H,bq); m/e 370 $(M+H)^+$; calculated for $C_{20}H_{23}N_3O_4$. 2HCl. 1.25 H_2O: C, 51.7; H, 5.9; N, 6.0. found: C, 51.6; H, 6.0; N, 9.2%.

EXAMPLE 108: 4-[[1-(4-pyridyl)piperidin-4-yl]aminocarbonyl]phenoxyacetic acid dihydrochloride

Following the method of Example 107, but starting from tertiary butyl 4-[[1-(4-pyridyl)piperidin-4-yl]aminocarbonyl]phenoxyacetate (50mg), but with the removal of the insoluble precipitate before freeze-drying, the title compound was prepared in 50% yield: m.p. 278-280°C; NMR(d_6DMSO + d_4 acetic acid) δ 8.19(2H,d), 7.82(2H,d), 7.20(2H,d), 6.98(2H,d), 4.74(2H,s), 4.23(3H,m), 3.38(2H,bt), 2.04(2H,m), 1.64(2H,m); m/e 356 $(M+H)^+$; calculated for $C_{19}H_{21}N_3O_4$. 2HCl. 1.25 H_2O: C, 50.6; H, 5.7; N, 9.3. found: C, 50.6; H, 5.7; N, 9.2%.

The starting material were prepared as follows.

(i) Acetyl chloride (3.95ml) was added dropwise to a stirred solution of 4-aminol-benzylpiperidine (10.0g) and triethylamine (7.7ml) in dry dichloromethane (100ml) at 4°C. The mixture was allowed to reach ambient temperature and stirred for 16 hours. Water was then added, the organic phase separated and dried ($MgSO_4$), and removal of the solvent by evaporation gave 4-acetylamino-1-benzylpiperidine, 10.23g, as a light brown solid which was used without further purification: NMR ($CDCl_3$) δ 7.29(5H,m), 5.29(1H,b), 3.79(1H,m), 3.49(2H,s), 2.80(2H,dm), 2.12(2H,dt), 1.95(3H,s), 1.91(2H,dm), 1.46(2H,dq); m/e 233 $(M+H)^+$.

(ii) 10% w/w Palladium on charcoal (1.5g) was added to a solution of the product from step (i) (10.0g), 1 molar hydrochloric acid (21.5ml) and methanol (150ml) and the mixture hydrogenated at room temperature and pressure until the theoretical amount of hydrogen had been taken up. Charcoal was added, the mixture stirred for 1 hour then filtered through diatomaceous earth and the filtrate evaporated to dryness giving 4-acetylaminopiperidine hydrochloride, 8.64g, as a sticky foam: NMR ($CDCl_3$ + d_6DMSO). δ 9,72(1H,b), 9.02(1H,b), 7.40(1H,bd), 3.87(1H,m), 3.30(2H,m), 2.81(2H,m), 1.86(4H,m), 1.80(3H,s); m/e 143 $(M+H)^+$.

(iii) A mixture of the product from step (ii) (1.79g), 4-chloropyridine hydrochloride (1.50g), sodium hydrogen carbonate (2.86g) in 3-methyl 1-butanol (25ml) was heated at reflux temperature for 16 hours. The cooled mixture was filtered and the filtrate concentrated in vacuo. Purification of the residue by flash chromatography on silica, eluting with methanol/dichloromethane (1:2 v/v) gave 4-acetylamino-1-(4-pyridyl)piperidine as a foam, 0.69g: NMR(d_6DMSO) δ 8.10(2H,d), 7.80(1H,bd), 6.80(2H,dd), 3.82(3H,m), 2.93(2H,dt), 1.78(3H,s), 1.77(2H,m), 1.33(2H,dq); m/e 220 $(M+H)^+$.

(iv) The product from step (iii) (0.52g) in 1 molar hydrochloric acid (11.9ml) was heated at 95°C for 5 hours. The solvent was evaporated and the residue, on drying over potassium hydroxide in vacuo gave 4-amino-1-(4-pyridyl)piperidine trihydrochloride hydrate, 0.70g as a light brown solid: m.p. >300°C; NMR (d_6DMSO) δ 8.28(4H,m), 7.22(2H,d), 4.27(2H,bd), 3.5 to 3.15(3H + H_2O), 2.09(2H,m), 1.59(2H,dq); m/e 178$(M+H)^+$; calculated for $C_{10}H_{15}N_3$. 3HCl. 0.75 H_2O: C, 40.0; H, 6.5; N, 14.0. found: C, 40.4; H, 6.3; N, 13.5%.

(v) A mixture of benzyl 4-hydroxybenzoate (4g), t-butyl bromoacetate (3.7g), powdered anhydrous potassium carbonate (2.4g) and acetone (100ml) was heated at reflux for 3 days. The reaction mixture was cooled and then filtered and the filtrate evaporated to dryness to give a viscous oil (6.37g). A portion of this oil (3.4g) was dissolved in methanol (30ml) and ammonium formate (4g) was added. The resultant solution was covered with a blanket of argon before a slurry of 10% Pd on C (100mg) in methanol (5ml), also under argon, was added. The reaction mixture was stirred at room temperature for 18 hours then the catalyst was filtered off through a pad of kieselguhr and washed with ethanol and water. The combined filtrate and washings were evaporated to dryness and the residue was partitioned between dichloromethane and aqueous sodium bicarbonate. The aqueous layer was separated, washed with dichloromethane and then carefully acidified with dilute aqueous citric acid solution. A solid precipitated which was collected, washed with water and air-dried to give 4-t-butoxycarbonylmethoxybenzoic acid (1.45g), as a white crystalline solid: m.p. 119-121°C.

(vi) Following the method of Example 106, but starting from the product of step (v) and the product from step (iv) and purification by flash chromatography on silica eluting with 0-5% v/v methanol/dichloromethane there was obtained tertiary butyl 4-[[1-(4-pyridyl)piperidin-4-yl]aminocarbonyl]phenoxyacetate hexafluorophosphate in 49% yield as a white solid: m.p. 196-198°C; NMR(d_6DMSO) δ 8.21(2H,d), 8.18(1H,d), 7.80(2H,d), 7.19(2H,d), 6.95(2H,d), 4.72(2H,s), 4.20(3H,m), 3.5-3.1(4H + H_2O), 1.98(2H,m), 1.59(2H,m), 1.42(9H,s); m/e 412 $(M+H)^+$; calculated for $C_{23}H_{29}N_3O_4$. HPF_6: C, 49.6; H, 5.4; N, 7.5. found: C, 49.1; H, 5.5; N, 7.3%. The free base was generated by flash chromatography on neutral alumina eluting with 1% v/v methanol dichloromethane and used in the preparation of the acid.

EXAMPLE 109: 4-[[1-(4-pyridyl)piperidin-4-yl]methylaminocarbonyl]phenoxyacetic acid

Following the method of Example 107, but starting from tertiary butyl 4-[[1-(4-pyridyl)piperidin-4-yl]methylaminocarbonyl]phenoxyacetate, the title compound was prepared in 95% yield: m.p. 84-86°C; NMR (d_6DMSO) δ 8.38(1H,t), 8.18(2H,d), 7.81(2H,d), 7.19(2H,d), 6.95(2H,d), 4.73(2H,s), 4.20(2H,bd), 3.8 to 3.0(H_2O), 1.99(1H,m), 1.84(2H,bd), 1.21(2H,m); m/e 370 $(M+H)^+$.

The starting material was prepared as follows:-

(i) Following the method of Example 108 step (i), but starting from 1-tertiarybutyloxycarbonylpiperidin-4-ylmethylamine tosylate there was prepared N-[(1-tertiarybutyloxycarbonylpiperidin-4-yl)methyl]acetamide in 95% yield as an oil which slowly crystallised: NMR ($CDCl_3$) δ 5.52(1H,b), 4.12(2H,bd), 3,14(2H,m), 2.68(2H,dt), 1.98(3H,s), 1.67(3H,m), 1.44(9H,s), 1.12(2H,dq); m/e 257 $(M+H)^+$.

The product was used in step (ii) without further purification.

(ii) A solution of the product from step (i) (6.50g) in trifluoroacetic acid (50ml) was stirred overnight. The solvent was evaporated and the residue, on purification by flash chromatography on neutral alumina, eluting with 10% v/v methanol/dichloromethane gave N-[4-piperidinylmethyl]acetamide, 3.78g, as a yellow oil: NMR (d^4 acetic acid) δ 3.22(2H,bd), 2.96(2H,d), 2.81(2H,dt), 1.83(3H,s), 1.76(2H,bd), 1.67(1H,m), 1.26(2H,dq); m/e 157 $(M+H)^+$.

(iii) Following the method of Example 106 step (i), but starting from the product of (ii) above and purification by flash chromatography on silica eluting with 20 to 33% v/v methanol/dichloromethane there was obtained 4-(4-acetylaminomethylpiperidin-1-yl)pyridine in 28% yield as a gummy solid: NMR (d_6DMSO) δ 8.18(2H,d), 7.90(1H,t), 7.07(2H,d), 4.12(2H,bd), 3.05(2H,dt), 2.95(2H,t), 1.80(3H,s), 1.77(3H,m), 1.13(2H,m); m/e 234 $(M+H)^+$.

(iv) Following the method of Example 108 step (iv), but starting from the product of (iii) above, there was obtained 4-(4-aminomethylpiperidin-1-yl)pyridine in 95% yield as a yellow gum: NMR (d_6DMSO) δ 8.26(4H,m), 7.21(2H,d), 4.26(2H,bd), 3.19(2H,dt), 2.74(2H,t), 2.05(1H,m), 1.92(2H,bd), 1.26(2H,dq); m/e 192 $(M+H)^+$.

(v) Following the method of Example 106, but starting from the product of Example 108 step (v) and the product from step (iv) above and purification by flash chromatography on silica, eluting with 0 to 5% v/v methanol/dichloromethane and trituration with diethyl ether there was obtained tertiary butyl 4-[[1-(4-pyridyl)piperidin-4-yl)]methylaminocarbonyl]phenoxyacetate hexafluorophosphate in 35% yield as a white solid: m.p. 182-184°C; NMR (d_6DMSO) δ 13.11(1H,b), 8.37(1H,t), 8.17(2H,d), 7.80(2H,d), 7.19(2H,d), 6.95(2H,d), 4.72(2H,s), 4.21(2H,bd), 3.19(4H,m), 2.00(1H,m), 1.86(2H,m), 1.43(9H,s), 1.21(2H,m); m/e 426$(M+H)^+$; calculated for $C_{24}H_{31}N_3O_4$. HPF_6. 0.5 H_2O: C, 49.6; H, 5.7; N, 7.2; P, 5.4. found: C, 49.6; H, 5.7; N, 7.1; P, 5.8%.

EXAMPLE 110: 4-[[1-(4-pyridyl)piperadin-4-yl]carboxamido]phenylacetic acid

Following the method of Example 2, but starting from methyl 4-[[1-(4-pyridyl)piperidin-4-yl]carboxamido]phenylacetate hydrochloride the title compound was prepared in 93% yield: m.p. 281-282°C; NMR (d_6DMSO) δ 9.87(1H,s), 8.13(2H,d), 7.51(2H,d), 7.16(2H,d), 6.83(2H,dd), 4.00(2H,dm), 3.49(2H,s), 2.90(2H,dt), 2.61(1H,m), 1.87(2H,dd), 1.66(2H,dq); m/e 340 $(M+H)^+$; calculated for $C_{19}H_{21}N_3O_3$: C, 67.2; H, 6.2; N, 12.4. found: C, 67.4; H, 6.2; N, 12.4%.

The starting material was prepared as follows:-

(i) Following the method of Example 104, but starting from methyl 4-aminophenylacetate hydrochloride, methyl 4-

[[1-(4-pyridyl)piperidin-4-yl]carboxamido]phenylacetate hydrochloride was prepared in 78% yield: m.p. 235-236.5°C; NMR (d_6DMSO) δ 13.61(1H,b), 10.10(1H,s), 8.21(2H,d), 7.55(2H,d), 7.21(2H,d), 7.16(2H,d), 4.28(2H,dm), 3.60(5H,s), 3.30(2H,m + H_2O), 2.81(1H,m), 1.98(2H,m), 1.67(2H,m); m/e 354$(M+H)^+$; calculated for $C_{20}H_{23}N_3O_3$. HCl: C, 61.6; H, 6.2; N, 10.8. found: C, 61.7; H, 6.3; N, 10.6%.

EXAMPLE 111: 4-Methyloxycarbonylmethylaminophenyl [1-(4-pyridyl)piperidin-4-yl]acetate

Thionyl chloride (1ml) was added dropwise to a stirred suspension of [1-(4-pyridyl)piperidin-4-yl]acetic acid (300mg) in dry dichloromethane (5ml) and the mixture stirred for 4 hours. The solvent was evaporated and the residue triturated with hexane and dried under high vacuum over potassium hydroxide to give a solid foam.

A solution of the foam in dry dichloromethane (5ml) was added dropwise to a stirred solution of methyl N-(4-hydroxyphenyl)glycinate (210mg) and triethylamine (0.33ml) in dry dichloromethane (10ml) and the mixture stirred for 16 hours. The mixture was diluted with dichloromethane, washed with water, dried and evaporated. Purification by flash chromatography on silica, eluting with 0 - 10% v/v methanol/dichloromethane and trituration of the resulting gum with diethyl ether gave the title compound, 80mg, as a white solid: m.p. 120-122°C; NMR(d_6DMSO), δ 8.13(2H,d), 6.84(2H,d), 6.81(2H,d), 6.54(2H,d), 6.01(1H,t), 3.96(2H,bd), 3.90(2H,d), 3.66(3H,s), 2.90(2H,dt), 2.50(2H,d + DMSO), 2.07(1H,m), 1.81(2H,bd), 1.30(2H,dq); m/e 384$(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4$. 0.5 H_2O: C, 64.3; H, 6.6; N, 10.7. found: C, 64.2; H, 6.3; N, 10.7%.

EXAMPLE 112: Methyl 4-[2-[1-(4-pyridyl)piperidin-4-yl]acetyl]phenoxyacetate

Oxalyl chloride (2.40 ml) was added to a stirred suspension of [1-(4-pyridyl)piperidin-4-yl]acetic acid hydrochloride hydrate (1.25 g) in dry dichloromethane under argon. A few drops of dry DMF were added and the mixture stirred for 30 minutes to give a clear solution. The solvent was removed in vacuo and the residue dried. The resulting solid foam was suspended in dichloroethane (40 ml), the suspension cooled to 4°C and with stirring, aluminium chloride (3.21 g) added. After 30 minutes the mixture was allowed to warm to ambient temperature when methyl phenoxyacetate (1.16 ml) was added and stirring continued for a further 2.5 hours. The mixture was added to an ice-water mixture to which was added dichloromethane. The aqueous phase was adjusted to pH7 and the solid removed by filtration. The filtrate was extracted three times with dichloromethane and the extracts dried ($MgSO_4$). Evaporation of the solvent gave a clear oil which crystallised on addition of ether. The solid was collected and on recrystallisation from methyl acetate gave the title compound, 1.06 g: m.p. 137-138°C; NMR (d_6DMSO) δ 8.11 (2H, b). 7.94 (2H, d), 7.03 (2H, d), 6.78 (2H, bd), 4.91 (2H, s), 3.90 (2H, d), 3.71 (3H, s), 2.91 (2H, d), 2.85 (2H, dt), 2.12 (1H, m), 1.75 (2H, bd), 1.26 (2H, dq); m/e 369 $(M+H)^+$; calculated for $C_{21}H_{24}N_2O_4$: C, 68.5; H, 6.6; N, 7.6. found C, 68.2; H, 6.5; N, 7.5%.

The starting [1-(4-pyridyl)piperidin-4-yl]acetic acid hydrochloride hydrate is described in Example 106 steps (i) and (ii).

EXAMPLE 113: 4-[2-[1-(4-pyridyl)piperadin-4-yl]acetyl]phenoxyacetic acid hydrochloride.

A mixture of the product of Example 112 (300 mg), dioxan (10 ml) and 1 solar hydrochloric acid (2.7 ml) were stirred for 80 hours at ambient temperature. The solvent was removed in vacuo and a little water added. The resulting solid was collected, washed with water and, after drying, gave the title compound, 170 mg: m.p. 239-241°C; NMR (D_2O) δ 8.17 (2H, d), 8.15 (2H, d), 7.36 (2H, d), 7.20 (2H, d), 5.01 (2H, s), 4.33 (2H, d), 3.38 (2H, dt), 3.16 (2H, d), 2.48 (1H, m), 2.08 (2H, d), 1.54 (2H, dq); m/e 355 $(M+H)^+$; calculated for $C_{20}H_{22}N_2O_4$.HCl.1.5H_2O: C, 57.4; H, 6.1; N, 6.7. found: C, 57.3; H, 6.1; N, 6.4%.

EXAMPLE 114: Methyl 4-[2-[4-(4-pyridyl)piperazin-1-yl]-2,2-dimethylacetyl]phenoxyacetate.

Methyl 4-(2,2-dimethylbromoacetyl)phenoxyacetate (1.58 g) was added to a stirred solution of 1-(4-pyridyl)piperazine (1.63 g) in acetonitrile (40 ml). After 34 days, the solid formed was removed by filtration and the filtrate evaporated to give an oil. Purification by flash chromatography on silica, eluting with 0.5 to 4.0% v/v methanol/ dichloromethane gave the title compound, 240 mg, as a white foam:

NMR (d_6DMSO) δ 8.49 (2H, d), 8.12 (2H, d), 6.96 (2H, d), 6.77 (2H, d), 4.87 (2H, s), 3.69 (3H, s), 3.28 (4H, t), 2.58 (4H, t), 1.25 (6H, s); m/e 398 $(M+H)^+$; calculated for $C_{22}H_{27}N_3O_4$.0.25H_2O: C, 65.7; H, 6.8; N, 10.4. found: C, 65.3; H, 6.9; N, 10.4%.

The necessary starting material was prepared as follows:-

(i) Following the method of Example 67 step (i) but starting from 4-(2,2-dimethylacetyl)phenol and only stirring for 18 hours instead of 2 days, there was obtained methyl 4-(2,2-dimethylacetyl)phenoxyacetate, in 90% yield, as an off-white crystalline solid: m.p. 45-46°C; NMR (d_6DMSO) δ 7.92 (2H, d), 7.02 (2H, d), 4.90 (2H, s), 3.71 (3H, s), 3.60 (1H, m), 1.09 (6H, d).

(ii) Bromine (2.09 ml) was added dropwise over ten minutes to a stirred solution of the product of step (i) above (9.44 g) in carbon tetrachloride (200 ml). The solution was stirred for 16 hours, then the solvent was evaporated in vacuo to give an orange oil. A solution of this oil, in a small volume of dichloromethane, was filtered through silica and the clear filtrate, on evaporation, gave methyl 4-(2-bromo-2,2-dimethylacetyl)phenoxyacetate, 11.3 g, as a white crystalline solid: m.p. 46-50°C; NMR (d_6DMSO) δ 8.09 (2H, d), 7.05 (2H, d), 4.92 (2H, s), 3.72 (3H, s), 2.00 (6H, s).

EXAMPLE 115: 4-[2-[4-(4-pyridyl)piperazin-1-yl]-2,2-dimethylacetyl]phenoxyacetic acid.

Following the method of Example 2 but starting from the product of Example 114 and stirring for 16 hours instead of 2 hours, the title compound was obtained in 76% yield, as a white crystalline solid: m.p. 278-279°C; NMR (D_2O) δ 8.72 (2H, d), 8.20 (2H, d), 7.16 (4H, d), 4.76 (2H, s), 3.80 (4H, bt), 2.91 (4H, bt), 1.55 (6H, s); m/e 406 $(M+Na)^+$, 384 $(M+H)^+$; calculated for $C_{21}H_{25}N_3O_4.0.5NaCl$: C, 61.1; H, 6.1; N, 10.2. found: C, 60.8; H, 5.9; N, 10.0%.

EXAMPLE 116: RS Methyl 4-[3-[4-(4-pyridyl)piperazin-1-yl]-2-methylpropanoyl]phenoxyacetate.

A stirred mixture of methyl 4-(2,2-dimethylbromoacetyl)phenoxyacetate (3.15 g), and 1-(4-pyridyl)piperazine (3.26 g) in acetonitrile (200 ml) was heated at reflux temperature for 4 days. The solvent was removed in vacuo and the residue partioned between dichloromethane/water. The organic phase was dried ($MgSO_4$), evaporated and then purified by flash chromatography on silica, eluting with 2 to 5% v/v methanol/dichloromethane. Further purification by flash chromatography on neutral alumina, eluting with dichloromethane, gave the title compound, 350 mg, as a clear oil: NMR (d_6DMSO) δ 8.12 (2H, d), 7.98 (2H, d), 7.04 (2H, d), 6.75 (2H, d), 4.92 (2H, s), 3.86 (1H,m), 3.71 (3H, s), 3.19 (4H, t), 2.70 (1H, q), 2.49 (DMSO+4H), 2.36 (1H, q), 1.09 (3H, s), trace of dichloromethane; m/e 398 $(M+H)^+$; calculated for $C_{22}H_{27}N_3O_4.0.1\ CH_2Cl_2$: C, 65.3; H, 6.7; N, 10.3. found: C, 65.1; H, 6.9; N, 10.1%.

EXAMPLE 117: Methyl 4-[4-[4-(4-pyridyl)piperazin-1-yl]methylphenyl]butyrate.

1-(4-Pyridyl)piperazine (1.63 g) was dissolved in warm acetonitrile (25 ml), the solution cooled to 30°C and with stirring, a solution of methyl 4-(4-bromomethylphenyl)butyrate in acetonitrile (5 ml) added. After 30 minutes the resulting precipitate was removed by filtration and the filtrate concentrated in vacuo to give a yellow oil. Purification by flash chromatography on silica, eluting with 0 to 4% v/v methanol/dichloromethane gave a solid. Trituration with ether and removal of the insoluble solid gave a clear solution. Concentration of this solution gave the title compound, 0.90 g, as a white fluffy solid: m.p. 126-127°C; NMR (d_6DMSO) δ 8.14 (2H, d), 7.24 (2H, d), 7.14 (2H, d), 6.77 (2H, d), 3.59 (3H, s), 3.48 (2H, s), 3.30 (4H, t), 2.59 (2H, t), 2.47 (4H, t), 2.32 (2H, t), 1.63 (2H, m); m/e 354 $(M+H)^+$; calculated for $C_{21}H_{27}N_3O_2.0.25H_2O$: C, 70.4; H, 7.7; N, 11.7.
found: C, 70.6; H, 7.6; N, 11.7%.

EXAMPLE 118: Methyl 5-[4-[4-(4-pyridyl)piperazin-1-yl]methylphenyl]pentanoate.

A mixture of methyl 5-(4-bromomethylphenyl)pentanoate and 5-(2-bromomethylphenyl)pentanoate, 70:30 w/w by NMR, prepared according to the method for the starting material in Example 117 (2.14 g) was reacted in a similar manner to Example 117. The crude mixture of esters was purified by flash chromatography on silica, eluting with 0-5% v/v methanol/dichloromethane. Evaporation of the appropriate fractions gave the title compound, 605 mg, as a waxy solid: m.p. 53-54°C; NMR (d_6DMSO) δ 8.13 (2H, d), 7.23 (2H, d), 7.14 (2H, d), 6.79 (2H, d), 3.58 (3H, s), 3.47 (2H, s), 3.30 (4H, t + H_2O), 2.57 (2H, t), 2.46 (4H, t), 2.32 (2H, t), 1.56 (4H, m); m/e 368 $(M+H)^+$; calculated for $C_{22}H_{29}N_3O_2.0.5H_2O$: C, 70.1; H, 8.0; N, 11.2. found: C, 70.3; H, 8.2; N, 11.0%.

EXAMPLE 119: 4-[4-[4-(4-pyridyl)piperazin-1-yl]methylphenyl]butyric acid, dihydrochloride.

Following the method of Example 71 but starting from the product of Example 118 and heating at 100°C for 4 hours instead of 1.5 hours the title compound was prepared in 88% yield: m.p. 236-238°C; NMR (D_2O) δ 8.40 (2H, d), 7.66 (2H, d), 7.61 (2H, d), 7.36 (2H, d), 4.61 (2H, s), 4.19 (4H, b), 3.69 (4H, b), 2.94 (2H, t), 2.61 (2H, t), 2.15 (2H, m); m/e 340 $(M+H)^+$; calculated for $C_{20}H_{25}N_3O_2.2HCl.0.5H_2O$: C, 57.0; H, 6.6; N, 10.0. found: C, 57.2; H, 6.9; N, 9.8%.

EXAMPLE 120: Mixture of 5-[4-[4-(4-pyridyl)piperazin-1-yl]methylphenyl]pentanoic acid and 5-[2-[4-(4-pyridyl)piperazin-1-yl]methylphenyl]pentanoic acid, dihydrochloride (4:1).

Following the method of Example 119, but starting from the crude mixture of esters in Example 118, there was obtained the title mixture of compounds in 59% yield, as a white solid: NMR (D_2O) δ 8.38 (2H, d), 7.62 (4H, m), 7.35 (2H, d), 4.70 (0.4H, s), 4.61 (1.6H, s), 4.18 (4H, b), 3.68 (4H, b), 2.98 (0.4H, t), 2.91 (1.6H, t), 2.59 (2H, t), 1.82 (4H, m); m/e 354 $(M+H)^+$; calculated for $C_{21}H_{27}N_3O_2$.2HCl.0.5H_2O: C, 57.9; H, 6.9; N, 9.7. found: C, 59.6; H, 7.2; N, 9.4%.

EXAMPLE 121: Ethyl 6-[4-(4-pyridylamino)phenoxy]hexanoate.

Trifluoroacetic acid (3 ml) was added to a stirred solution of ethyl 6-[4-[N-(4-pyridyl)-N-tertiary-butyloxycarbonylamino]phenoxy]hexanoate (260 mg) dissolved in dichloromethane (3 ml). After 18 hours the solvents were removed in vacuo and the residual gum dissolved in dichloromethane. This solution was treated with a saturated solution of sodium hydrogen carbonate. The organic phase was washed with water, dried and evaporated. Trituration of the residue with hexane gave the title compound, 120 mg, as a white solid: m.p. 104-106°C; NMR ($CDCl_3$) δ 8.22 (2H, d), 7.12 (2H, d), 6.90 (2H, d), 6.64 (2H, dd), 5.82 (1H, s), 4.13 (2H, q), 3.97 (2H, t), 2.34 (2H, t), 1.80 (2H, m), 1.70 (2H, m), 1.53 (2H, m), 1.27 (3H, t); m/e 329 $(M+H)^+$; calculated for $C_{19}H_{24}N_2O_3$.0.25H_2O:C, 68.6; H, 7.4; N, 8.4. found: C, 68.8; H, 7.3; N, 8.2%.

The necessary starting material was prepared as follows:-

(i) A stirred mixture of 4-chloropyridine hydrochloride (2 g) and 4-methoxyaniline (4.9 g) was heated at 140°C for 5 hours. After cooling the residue was dissolved in dichloromethane (250 ml), the solution extracted with water (2x100 ml). The aqueous extracts were treated with sodium hydroxide solution and then extracted with ethyl acetate (4x100 ml). The combined organic extracts were washed with water, and saturated sodium chloride solution, then dried and the solvent evaporated. Purification by flash chromatography on silica, eluting with 10% v/v methanol/dichloromethane gave 4-(4-pyridylamino)methoxybenzene, 2 g, as a fawn solid: m.p. 159-160°C; NMR (d_6DMSO) δ 8.47 (1H, s), 8.09 (2H, d), 7.10 (2H, d), 6.92 (2H, d), 6.70 (2H, dd), 3.73 (3H, s); m/e 201 $(M+H)^+$; calculated for $C_{12}H_{12}N_2O_3$: C, 72.0; H, 6.0; N, 14.0. found: C, 71.4; H, 6.1; N, 13.8%.

(ii) A mixture of the product from step (i) above (2.0 g) and 48% w/v hydrobromic acid (30 ml) was heated at 140°C for 4 hours. The cooled solution was neutralised with 0.880 ammonia solution and then extracted four times with ethyl acetate. The combined organic extracts were washed with water and saturated sodium chloride solution, then dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica, eluting with 10 to 20% v/v methanol/dichloromethane gave 4-(4-pyridylamino)phenol, 0.78 g as an off-white solid: m.p. 246-248°C; NMR ($CDCl_3$+d_6DMSO) δ 8.92 (1H, b), 8.09 (2H, d), 7.31 (1H, s), 7.00 (2H, d), 6.79 (2H, d), 6.67 (2H, dd); m/e 187 $(M+H)^+$.

(iii) A mixture of the product from step (ii) above (0.78 g), di-tertiary-butyl dicarbonate (0.91 g), triethylamine (0.59 ml), 1,2-dimethoxymethane (20 ml) and water (10 ml) was stirred for 18 hours. The solvents were removed in vacuo and the residue partitioned between ethyl acetate and water. The aqueous phase was extracted two times with further ethyl acetate and the combined organic extracts washed with water and brine, dried ($MgSO_4$) and evaporated to a small volume when crystallisation occurred. Collection by filtration gave 4-[N-(4-pyridyl)-N-tertiary-butyloxycarbonylamino]phenol, 1.07 g as a white crystalline solid: m.p. 192-194°C (dec); NMR ($CDCl_3$) δ 8.28 (2H, dd), 7.18 (4H, s), 6.76 (2H, dd), 6.03 (1H, bs), 1.57 (9H, s); m/e 287 $(M+H)^+$.

(iv) Sodium hydride (50% w/w dispersion in mineral oil, 55 mg) was added under argon to a stirred solution of the product from step (iii) above (300 mg) in dry DMF (5 ml). After five minutes, ethyl 6-bromohexanoate (0.20 ml) was added and the mixture stirred for 16 hours. The DMF was evaporated in vacuo and the residue partitioned between dichloromethane and water. The aqueous phase was extracted with further dichloromethane. The combined organic extracts were washed with water then dried, and evaporated. The residue was purified by chromatography on alumina, eluting with dichloromethane and then 1% v/v methanol/dichloromethane. Evaporation of the appropriate fractions gave ethyl 6-[4-[N-(4-pyridyl)-N-tertiarybutyloxycarbonylamino]phenoxy]hexanoate, 260 mg, as a yellow gum: NMR ($CDCl_3$) δ 8.40 (2H, dd), 7.16 (2H, dd), 7.07 (2H, m), 6.90 (2H, m), 4.13 (2H, q), 3.98 (2H, t), 2.34 (2H, t), 1.78 (4H, m), 1.57 (2H, m), 1.44 (9H, s), 1.26 (3H, t); m/e 429 $(M+H)^+$.

EXAMPLE 122: 6-[4-(4-pyridylamino)phenoxy]hexanoic acid hydrochloride.

Following the method of Example 71, but starting from the product of Example 121 and heating at 100°C for 16 hours instead of 1.5 hours, the title compound was obtained in 80% yield as a freeze-dried solid: NMR (d_6DMSO) δ 13.63 (1H, b), 11.95 (1H, b), 10.49 (1H, s), 8.21 (2H, d), 7.26 (2H, d), 6.98 (4H, m), 4.00 (2H, t), 2.23 (2H, t), 1.70 (2H, m), 1.55 (2H, m), 1.45 (2H, m); m/e 301 $(M+H)^+$; calculated for $C_{17}H_{20}N_2O_2$.HCl. 1.25H_2O: C, 56.8; H, 6.6; N, 7.8.

found: C, 56.8; H, 6.6; N, 7.4%.

EXAMPLE 123: N-[4-[(4-pyridyl)piperazin-1-yl]benzoyl]-N-methylglycine, trifluoroacetate

To a solution of ethyl N-[4-[(4-pyridyl)piperazin-1-yl]benzoyl]-N-methylglycinate (78 mg) in methanol (2 ml) was added sodium hydroxide solution (1N, 0.4 ml) and the resultant mixture was stored at room temperature for 1 hour. The pH of the reaction mixture was adjusted to 2 by addition of 2N HCl (aq) (0.45 - 0.5 ml) and the resultant solution was purified by preparative rp-hplc on a DYNAMAX C-18, 60A [83-201-C] column using an acetonitrile/water mobile phase containing 0.1% trifluoroacetic acid, to give, after lyophilisation, the title compound (46 mg) as a glass: NMR (d_6-DMSO) δ 2.98 (3H, s), 3.45 (4H, m), 3.86 (4H, m), 4.07 (2H, s), 6.97 (2H, d), 7.23 (2H, d), 7.31 (2H, m), 8.27 (2H, d); m/Z 355 (M + H)$^+$; calculated for $C_{19}H_{22}N_4O_3$. 1.0 CF_3CO_2H. 1.25 H_2O: C, 51.4%; H, 5.24%; N, 11.4%; found: C, 51.2%; H, 4.9%; N, 11.2%.
The necessary starting material was prepared as follows:-

(i) To a stirred mixture of 4-[(4-pyridyl)piperazin-1-yl]benzoic acid (prepared as in Example 30(i)) (311 mg), HOBt.H_2O (170 mg) and HBTU (416 mg) in DMF (5 ml) at 0-5°C under argon was added diisopropylethylamine (0.75 ml). The ice-bath was removed and the reaction mixture was stirred at room temperature for 15 minutes before solid sarcosine, ethyl ester hydrochloride (154 mg) was added. The reaction mixture was stirred at room temperature under argon overnight then diluted with dichloromethane (30 ml) and water (30 ml). The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (30 ml). The combined organic extracts were washed with water, saturated sodium bicarbonate solution, water, dried ($MgSO_4$) and evaporated. The residue was purified by filtration through a short bed of activated (grade II) alumina by elution with ethyl acetate/methanol, 5:1, to give ethyl N-(4-[(4-pyridyl)piperazin-1-yl]benzoyl)-N-methylglycinate (92 mg) as an amorphous solid: NMR (d_6-DMSO + CD_3CO_2D) δ 1.18 (3H, t), 2.98 (3H, s), 3.44 (4H, m), 3.79 (4H, m), 4.11 (4H, m), 6.94 (2H, d), 7.12 (2H, d), 7.31 (2H, br, d), 8.19 (2H, d); m/Z 383 (M + H)$^+$.

EXAMPLE 124: N-[4-[(4-pyridyl)piperazin-1-yl]benzoyl]-L-phenylalanine, methyl ester

In a similar manner to Example 123 (i), 4-[(4-pyridyl)piperazin-1-yl]benzoic acid (311 mg), p-toluene sulphonic acid, monohydrate (418 mg), HOBt.H_2O (170 mg), HBTU (416 mg), DMF (5 ml), diisopropylethylamine (1.13 ml) and L-phenylalanine, methyl ester hydrochloride (216 mg) gave, after filtration through a bed of neutral alumina and elution with ethyl acetate/methanol, 6:1, the title compound as a white crystalline solid (336 mg): m.p. 139-143.5°C; NMR ($CDCl_3$) δ 3.26 (2H, m), 3.50 (8H, m), 3.76 (3H, s), 5.09 (1H, m), 6.46 (1H, d), 6.70 (2H, m), 6.90 (2H, d), 7.13 (2H, m), 7.28 (3H, m), 7.68 (2H, d), 8.31 (2H, m); m/z 445 (M + H)$^+$; calculated for $C_{26}H_{28}N_4O_3$. 1.0 H_2O: C, 67.5%; H, 6.54%; N, 12.1%; found: C, 67.6%; H, 6.4%; 12.1%.

EXAMPLE 125: N-[4-[(4-pyridyl)piperazin-1-yl]benzoyl]-L-phenylalanine

To a solution of the product of Example 124 (100 mg) in methanol (2.2 ml) was added sodium hydroxide solution (1N, 0.44 ml). The resultant mixture was stored at room temperature with occasional swirling for 2.5 hr, then the pH was adjusted to 5 by addition of 2N HCl (aq) (0.22 ml) and 50% aqueous acetic acid (3 drops). The mixture was filtered and evaporated to dryness. The residue was crystallised from hot water containing a trace of methanol to give the title compound as a pale yellow crystalline solid (47 mg): NMR (d_6-DMSO + CD_3CO_2D) δ 3.05 (1H, m), 3.15 (1H, m), 3.45 (4H, m), 3.77 (4H, m), 4.58 (1H, m), 6.90 (2H, d), 7.12 (2H, d), 7.22 (5H, m), 7.70 (2H, d), 8.19 (2H, d); m/Z 431 (M + H)$^+$; calculated for $C_{25}H_{26}N_4O_3$. 0.75 H_2O: C, 67.6%; H, 6.24%; N, 12.6%; found: C, 67.6%; H, 6.0%; N, 12.5%.

EXAMPLE 126: (S)-3-[N-[2-phenethyl]carboxamido]-3-[4-[4-(4-pyridyl)piperazin-1-yl]]benzamidopropionic acid

To a stirred suspension of benzyl (S)-3-[N-[2-phenethyl]carboxamido]-3-[4-[4-(4-pyridyl)piperazin-1-yl]]benzamidopropionate (120 mg) in methanol (3 ml) was added sodium hydroxide solution (1N, 0.5 ml). Within 15 minutes all the solids had dissolved, and the reaction mixture was stirred at room temperature for a further 2 hr. The pH was then adjusted to 5 by addition of 2N HCl (aq) (0.25 ml) and 50% aqueous acetic acid (3 drops). The mixture was filtered and evaporated to dryness. The residue was crystallised from hot water containing a trace of methanol to give the title compound as a pale yellow crystalline solid (66 mg): NMR (d_6-DMSO + CD_3CO_2D) δ 2.70 (4H, m), 3.30 (2H, t), 3.56 (4H, m), 3.85 (4H, m), 4.73 (1H, m), 6.99 (2H, d), 7.20 (7H, m), 7.80 (2H, d), 8.25 (2H, d); m/Z 502 (M + H)$^+$; calculated for $C_{28}H_{31}N_5O_4$. 1.25 H_2O: C, 64.2%; H, 6.44%; N, 13.4%; found: C, 64.2%; H, 6.4%; N, 13.6%.
The necessary starting material was prepared as follows:-

i) Boc-L-aspartic acid, 2-phenethylamide, β-benzyl ester (preparation described in Samanen, J. et al (1991), J. Med. Chem. 34, 3114-25) (2 g) was dissolved in a mixture containing dichloromethane (10 ml) and trifluoroacetic acid (10 ml). The resultant pale yellow solution was stored at room temperature for 2 hr after which time the mixture was evaporated to dryness. The oily product was dissolved in dry ether and re-evaporated. This procedure was repeated twice more to give a viscous oily residue containing the trifluoroacetate salt of L-aspartic acid, 2-phenethylamide, β-benzyl ester (2.07 g) which was used without further purification.

ii) In a similar manner to Example 123 (i), 4-[(4-pyridyl)piperazin-1-yl]benzoic acid (311 mg), p-toluene sulphonic acid, monohydrate (627 mg), HOBt.H_2O (170 mg), HBTU (416 mg), DMF (15 ml), diisopropylethylamine (1.5 ml) and L-aspartic acid, 2-phenethylamide, β-benzyl ester (440 mg) gave, after purification by flash chromatography on silica, eluting solvent, ethyl acetate/methanol, 4:1 to 2:1, benzyl (S)-3-(N-[2-phenethyl]carboxamido)-3-[4-[4-(4-pyridyl)piperazin-1-yl]]benzamidopropionate (268 mg) as a white crystalline solid: NMR (d_6-DMSO) δ 2.70 (2H, t), 2.76 (1H, m), 2.88 (1H, m), 3.25 (2H, m), 3.44 (4H, m), 3.50 (4H, m), 4.84 (1H, m), 5.08 (2H, s), 6.89 (2H, d), 7.02 (2H, d), 7.20 (5H, m), 7.31 (5H, m), 7.78 (2H, d), 7.90 (1H, t), 8.20 (2H, d), 8.36 (1H, d); m/Z 592 $(M + H)^+$; calculated for $C_{35}H_{37}N_5O_4$. 0.25 H_2O: C, 70.5%; H, 6.34%; N, 11.7%; found: C, 70.5%; H, 6.3%; N, 11.7%.

EXAMPLE 127: (R)-3-[N-[2-phenethyl]carboxamido]-3-[4-[4-(4-pyridyl)piperazin-1-yl]]benzamidopropionic acid

Following the method of Example 126, but starting from benzyl (R)-3-[N-[2-phenethyl]carboxamido]-3-[4-[4-(4-pyridyl)piperazin-1-yl]]benzamidopropionate instead of the corresponding (S)-isomer, the title compound was obtained as a pale yellow crystalline solid in 33% yield: NMR (d_6-DMSO + CD_3CO_2D) δ 2.71 (4H, m), 3.29 (2H, t), 3.53 (4H, m), 3.83 (4H, m), 4.72 (1H, m), 6.99 (2H, d), 7.17 (7H, m), 7.77 (2H, d), 8.24 (2H, d); m/Z 502 $(M + H)^+$; calculated for $C_{28}H_{31}N_5O_4$. 1.25 H_2O: C, 64.2%; H, 6.44%; N, 13.4%; found: C, 64.2%; H, 6.4%; N, 13.3%.
The necessary starting material was prepared as follows:-

i) Boc-D-aspartic acid, 2-phenethylamide, β-benzyl ester (preparation described in Rodriguez, M. et al (1989), J. Med. Chem. 32, 522-8) (1 g) was dissolved in acetonitrile (5 ml) with gentle warming, then cooled to room temperature before excess ethereal HCl (5 ml) was added. The reaction mixture was stored at room temperature overnight then evaporated to dryness. The pale yellow oily residue was triturated with dry ether and re-evaporated. This procedure was repeated twice more to give a hygroscopic oily residue containing the hydrochloride salt of D-aspartic acid, 2-phenethylamide, β-benzyl ester (0.55 g) which was used without further purification.
ii) In a similar manner to Example 30 the hydrochloride salt of D-aspartic acid, 2-phenethylamide, β-benzyl ester (363 mg), 4-[(4-pyridyl)piperazin-1-yl]benzoyl chloride (377 mg), diisopropylethylamine (0.87 ml) and DMF (5 ml) gave benzyl (R)-3-[N-[2-phenethyl]carboxamido]-3-[4-[4-(4-pyridyl)piperazin-1-yl]]benzamidopropionate (510 mg) as an off-white, amorphous solid: m/Z 592 $(M + H)^+$.

EXAMPLE 128: 4-oxo-4-[4-[4-(4-pyridyl)piperazin-1-yl]phenyl]aminobutyric acid

To a solution of 1-(4-aminophenyl)-4-(4-pyridyl)piperazine (100 mg) in DMF (8 ml) was added succinic anhydride (79 mg). The reaction mixture was stirred at room temperature for 2.5 hr and a precipitate was collected, washed with DMF and ethanol, then dried to give the title compound (106 mg) as a beige-coloured solid: m.p. 263-264°C; NMR (d_6-DMSO + CF_3CO_2H) δ 2.68 (4H, m), 3.80 (4H, m), 4.19 (4H, m), 7.20 (2H, d), 7.56 (2H, d), 7.82 (2H, d), 8.21 (2H, d), 9.62 (1H, s); m/Z 355 $(M + H)^+$; calculated for $C_{19}H_{22}N_4O_3$. 0.4 H_2O: C, 63.1%; H, 6.36%; N, 15.5%; found: C, 63.1%; H, 6.4%; N, 15.7%.
The necessary starting material was prepared as follows:-

(i) To an intimate mixture of 4-[(4-pyridyl)piperazin-1-yl]benzoic acid (Example 30(i)) (500 mg) and hydroxylamine hydrochloride (13.5 mg) was added polyphosphoric acid (16 g). The resultant mixture was heated to 160°C and maintained at that temperature with stirring for 30 min. The mixture was then allowed to cool to approximately 100°C before crushed ice, followed by 15% potassium hydroxide solution to give a pH 11 of were added. The suspension was allowed to cool to room temperature and the precipitate was collected, washed with water and air-dried to give 1-(4-aminophenyl)-4-(4-pyridyl)piperazine (159 mg) as a light brown solid: m.p. 204-208°C; NMR (d_6-DMSO) δ 3.00 (4H, m), 3.41 (4H, m), 4.65 (2H, br. s), 6.51 (2H, d), 6.73 (2H, m), 6.85 (2H, d), 8.18 (2H, d); m/Z 255 $(M + H)^+$.

EXAMPLE 129: 4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyric acid, hydrochloride salt

A mixture of the product from Example 26 (1.5 g) and methanol (80 ml) was heated to reflux with stirring, and solid pyridine hydrochloride (0.5 g) was added. Heating was stopped and ethyl acetate (10 ml) was added. The reaction mixture was evaporated until a slight turbidity was observed. On further cooling, a precipitate formed which was collected, washed with ethyl acetate and dried to give the title compound (1.33 g) as a beige solid: m.p. >240°C (dec); NMR (d_6-DMSO) δ 1.90 (2H, m), 2.36 (2H, t), 3.17 (4H, m), 3.83 (4H, m), 3.91 (2H, t), 6.89 (4H, q), 7.26 (2H, d), 8.25 (2H, d), 12.1 (1H, br), 13.75 (1H, br); m/Z 342 (M + H)$^+$; calculated for $C_{19}H_{23}N_3O_3$. 1.0 HCl: C, 60.4%; H, 6.4%; N, 11.1%; found: C, 60.0%; H, 6.4%, N, 10.8%.

EXAMPLE 130: N-2-methoxyethyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyramide, trifluoroacetate

A solution of methoxyethylamine (0.9 ml) in dry dichloromethane (5 ml) was added dropwise to a stirred solution of trimethylaluminium, 2M in toluene (5 ml) at 5-10°C under argon. On completion of the addition, the ice-bath was removed and the reaction mixture was stirred at room temperature for 1 hr before a solution of the product of Example 25 (0.62 g) in dichloromethane (5 ml) was added dropwise. The reaction mixture was heated to reflux under argon and stirred at reflux for 2 hr. The reaction mixture was then cooled to room temperature and diluted with dichloromethane (20 ml). A solution of methanol/dichloromethane, 1:1 (3 ml) was then added dropwise with stirring. The reaction mixture was further diluted with dichloromethane (10 ml), methanol, (3 ml) and water (5 ml). The organic layer was separated, dried (Na_2SO_4) and evaporated to dryness. The residue was purified by preparative rp-hplc on a DYNAMAX C-18, 60A [83-201-C] column using an acetonitrile/water mobile phase containing 0.1% trifluoroacetic acid, to give, after lyophilisation, the title compound (56 mg) as an off-white solid: NMR (d_6-DMSO) δ 1.89 (2H, m), 2.22 (2H, t), 3.18 (6H, m), 3.23 (3H, s), 3.32 (2H, t), 3.85 (6H, m), 6.90 (4H, q), 7.28 (2H, d), 7.88 (1H, br. t), 8.25 (2H, d); m/Z 399 (M + H)$^+$; calculated for $C_{22}H_{30}N_4O_3$. 1.7 CF_3CO_2H: C; 51.5%; H, 5.4%; N, 9.5%; found: C, 51.4%; H, 5.6%; N, 9.3%.

EXAMPLE 131: 4-[2-[4-(4-pyridyl)piperazin-2-one-1-yl]acetyl]phenoxyacetic acid monohydrochloride

A solution of methyl 4-[2-(piperazin-2-one-1-yl)acetyl]phenoxyacetate (0.347g), 4-chloropyridine hydrochloride (0.19g) and triethylamine (0.178g) in water (8ml) and dioxan (1ml) was heated on a steam bath for 2 hours and then evaporated to dryness. The residue was triturated with water (2ml) and filtered. The solid thus obtained was recrystallised from water to give the title compound (0.187g), m.p. 275-277°C; NMR(d_6DMSO δ8.33(2H,d), 8.0(2H,d), 7.21(2H,d), 7.1(2H,d), 4.97(2H,s), 4.81(2H,s), 3.94(2H,m), 3.59(2H,m); m/e 370(M+H)$^+$; calculated for $C_{19}H_{20}N_3O_5Cl$. 0,75 H_2O: C, 54.4; H, 5.0; N, 10.0. Found: C, 54.5; H, 5.3; N, 9.5%.

The necessary starting material was made as follows:-

(i) To a vigorously stirred mixture of piperazinone (3.23g), potassium carbonate (4.46g) in water (15ml) and tert butanol (15ml) at room temperature, was added portionwise over 5 minutes, di tert butyl dicarbonate (7.75g). The mixture was stirred for 2 hours. Ethyl acetate (20ml) was added to extract the solid thus formed and the organic layer separated, filtered through phase separating paper and evaporated. The solid residue was recrystallised from ethyl acetate to give 4-tert butoxycarbonylpiperazin-2-one (5.31g), m.p. 157-159°C; NMR(d_6DMSO) δ 8.0(1H,broad), 3.81(2H,s), 3.45(2H,t), 3.17(2H,m), 1.4(9H,s); m/e 207 (M+H)$^+$.

(ii) To a stirred suspension of the product of step i) (0.5g) in dry DMF (3ml) under an argon atmosphere, was added sodium hydride (60% dispersion in mineral oil, 0.1g). After 1 hour at room temperature, methyl 4-bromoacetylphenoxyacetate (0.72g) was added and the solution stirred for 1 1/2 hours. The mixture resulting was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and filtered through phase separating paper. Evaporation of the solvent gave an oil which was purified by flash column chromatography, the product being eluted with 1/1 v:v ethyl acetate/hexane to give methyl 4-([2-(4-tert-butoxycarbonyl)piperazin-2-one-1-yl]acetyl)phenoxyacetate as a solid (0.32g), m.p. 81-82°C; NMR($CDCl_3$) δ7.97(2H,m), 6.98(2H,m), 4.83(2H,s), 4.71(2H,s), 4.18(2H,s), 3.81(3H,s), 3.71(2H,t), 3.42(2H,t), 1.47(9H,s).

(iii) A solution of the product from step (ii) (2.2g) in TFA (10ml) was kept at room temperature for 1 hour and then evaporated to dryness. The residue was partitioned between ethyl acetate and aqueous sodium carbonate. The organic layer was filtered through phase separating paper and solvent evaporated. The residue was triturated with ethyl acetate to give a solid, m.p. 128 - 132°C. NMR(d_6DMSO) δ 7.95(2H,d), 7.06(2H,d), 4.9(2H,s), 3.7(3H,s), 3.3(2H,m), 2.9(2H,m).

EXAMPLE 132: RS 3-Methyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyric acid, trifluoroacetate

To a stirred suspension of 4-[(4-pyridyl)piperazin-1-yl]phenol (1.02g) in dry DMF (10ml) was added sodium hydride (60% dispersion in mineral oil, 0.16g) and the mixture stirred for 1 hour at room temperature. To the resulting solution was added ethyl-4-bromo-3-methylbutyrate and the mixture stirred for 16 hours. Solvent was evaporated and the residue partitioned between water and dichloromethane. Insoluble material was removed by centrifugation. The organic layer was filtered through phase separating paper (Whatman IPS) and the residue was purified by flash chromatography on silica gel by elution with methanol/dichloromethane/concentrated ammonia (50/950/5) to give ethyl 3-methyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyrate (0.27g) which was hydrolysed in methanol (3ml) and aqueous sodium hydroxide (1N, 2ml) for 2 hours at room temperature. The solution was evaporated and the residue purified by reverse phase h.p.l.c (water/acetonitrile/0.1% TFA gradient) to give a glass which crystallised on trituration with ether to give the title compound (0.08g): m.p. 169-171°C; NMR(d_6DMSO) δ 13.45(1H,broad), 12.07(1H,broad) 8.27(2H,d), 7.28(2H,d), 6.9(4H,m), 3.80(6H,m), 3.16(4H,t), 2.45(1H,m), 2.37(1H,m), 2.12(1H,m), 1.0(3H,d); m/e 356(M+H)$^+$; calculated for $C_{22}H_{25}N_3O_4F_3$. 0.5 H_2O: C, 55.2; H, 5.6; N, 8.9. Found: C, 55.3; H, 5.6; N, 8.7%.

EXAMPLE 133: RS-4-[4-(4-pyridyl)piperazin-1-yl]phenoxy-3-vinylbutyric acid, sodium salt

A solution of RS methyl 4-[4-(4-pyridyl)piperazin-1-yl]phenoxy-3-vinylbutyrate (0.29g) in 1N sodium hydroxide solution (2.3ml) and methanol (5ml) was kept at room temperature for 4 hours. The solution was evaporated and water (2ml) added to the solid residue. The solid thus obtained was filtered and washed with acetone and ether to give the title compound (0.042g): m.p. 293-295°C; NMR (d_6-DMSO) δ 8.18(2H,d), 6.9(6H,m), 5.88(1H,m), 4.96(2H,m), 4.0(1H,m), 3.77(1H,t), 3.41(2H,m), 3.10(2H,m), 2.84(1H,m), 1.98(2H,d), m/e 470(M+H)$^+$; calculated for $C_{21}H_{24}N_3O_3Na$. H_2O: C, 61.9; H, 6.4; N, 10.3. Found: C, 62.1; H, 6.4; N, 10.5%.

The necessary starting material was made as follows:-

(i) A solution of RS 3-vinylbutyrolactone (3.5g) and sodium acetate (2.56g) in methanol (30ml) was kept for 20 hours. Solvent was evaporated and the residue was partitioned between water and ether. The aqueous layer was extracted twice more with ether and the extracts combined, filtered through phase separating paper and evaporated. The residue was purified by filtration chromatography on silica gel (Merck 7736) starting with 1/9 ethyl acetate/hexane and progressing to 4/6 ethyl acetate/hexane as eluent to give methyl 4-hydroxy-3-vinylbutyrate as an oil; NMR($CDCl_3$) δ 5.73(1H,m), 5.15(2H,m), 3.68(3H,s), 3.60(2H,t), 2.76(1H,m), 2.48(2H,m), 1.69(1H,t); m/e 145(M+H)$^+$.

(ii) To a stirred suspension of 4-[(4-pyridyl)piperazin-1-yl]phenol (1.98g) in dichloromethane (30ml) at 15°C was added triphenylphosphine (2.04g) followed by dropwise addition of diethyl azodicarboxylate (1.35g). The mixture was stirred until complete solution was obtained. Methyl-4-hydroxy-3-vinylbutyrate (1.12g) was added dropwise and the mixture stirred for 4 hours. The solid which had precipitated during the reaction was the starting phenol and was filtered off. The filtrate was evaporated and the residue treated with ethyl acetate (20ml) and filtered. The filtrate was extracted with 2N hydrochloric acid (2 x 10ml) and the aqueous layer separated and basified with 0.89 S.G. ammonium hydroxide. The precipitate was extracted twice into ethyl acetate and the combined extracts filtered through phase separating paper and evaporated. The residue was purified by flash chromatography on silica gel, eluting with methanol/dichloromethane/0.89 S. G. ammonia hydroxide v:v:v 7.5/92.5/0.75 to give RS methyl 4-[4-(4-pyridyl)piperazin-1-yl]phenoxy-3-vinylbutyrate (0.29g); NMR($CDCl_3$) δ 8.3(2H,d), 6.88(4H,m), 6.70(2H,d), 5.85(1H,m), 5.20(2H,m), 3.90(2H,m), 3.67(3H,s), 3.48(2H,m), 3.18(2H,m), 3.06(1H,m), 2.68(1H,m), 2.47(1H,m), 1.80(1H,br); m/e 382 (M+H)$^+$.

EXAMPLE 134: Ethyl [2-allyl-4-[4-(4-pyridyl)piperazin-1-yl]]phenoxybutyrate

In a similar manner to Example 25 but starting from 2-allyl-4-[4-(4-pyridyl)piperazin-1-yl]phenol, the title compound was prepared in 50% yield as a solid, m.p. 53-55°C NMR($CDCl_3$) δ 8.3(2H,d), 6.83(1H,m), 6.79(2H,d), 6.71(2H,d.d), 6.0(1H,m), 5.1(2H,m), 4.15(2H,q), 3.98(2H,t), 3.49(4H,m), 3.39(2H,d), 3.19(4H,m), 2.53(2H,t), 2.11(2H,q), 1.76(3H,t), m/e 410(M+H)$^+$; calculated for $C_{24}H_{31}N_3O_3$.0.5 H_2O: C, 68.9; H, 7.7; N, 10.0. Found: C, 68.8; H, 7.7; N, 9.9%.

The necessary starting material was prepared as follows:-

(i) Sodium hydride (60% dispersion in mineral oil, 0.4g) was added to a stirred suspension of 4-[4-(4-pyridyl)piperazin-1-yl]phenol (2.55g) in DMF (25ml) and the mixture stirred for 20 minutes at room temperature. Allyl chloride (0.756g) was added dropwise and stirring continued for 20 hours. Ice-water (75ml) was added and the mixture extracted three times with ethyl acetate. The combined extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was triturated with hexane and filtered to give 4-[4-(4-pyridyl)piperazin-1-yl]phenol allyl ether (2.5g) as a solid; NMR(d_6DMSO) δ 8.18(2H,dd), 6.8-7.0(6H,m), 5.92-6.13(1H,m), 5.2-5.45(2H,m), 4.5(2H,m), 3.45(4H,m), 3.11(4H,m).

(ii) The product from step (i) (5g) was heated under argon in gently refluxing diphenyl ether (15g) for 2 1/2 hours.

The mixture was cooled to room temperature and ether (70ml) was added. The solid material was filtered and purified by flash chromatography on silica gel, eluting with methanol/dichloromethane (1/4 v/v) to give 2-allyl-4-[4-(4-pyridyl)piperazin-1-yl]phenol (0.88g) as a solid, m.p. 180 - 182°C; NMR (d_6-DMSO) δ 8.88(1H,s), 8.19(2H,dd), 6.87(2H,dd), 6.7(3H,m), 5.88-6.03(1H,m), 5.0(2H,m), 3.44(4H,t), 3.28(2H,d), 3.05(4H,t); m/e 296 $(M+H)^+$.

EXAMPLE 135: [2-allyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyric acid

In a similar manner to Example 26, but starting from the product of Example 134, the title compound was prepared as solid in 61% yield; m.p. 209-210°C (dec); NMR (d_6DMSO) δ 8.19(2H,d), 6.84(5H,m), 5.82-6.08(1H,m), 4.92-5.12(2H,m), 3.91(2H,t), 3.44(4H,t), 3.3(2H,d), 3.1(4H,t), 2.4(2H,t), 1.93(2H,t); m/e 382$(M+H)^+$; calculated for $C_{22}H_{27}N_3O_3$: C, 69.3; H, 7.13; N, 11.0. Found: C, 69.2; H, 7.3; N, 11.2%.

EXAMPLE 136: Ethyl-[2-n-propyl-4-[4-(4-pyridyl)piperazin-1-yl]]phenoxybutyrate

In a similar manner to Example 25, but starting from 2-n-propyl-4-[4-(4-pyridyl)piperazin-1-yl]phenol, the title compound was prepared in 24% yield as a solid, m.p. 65-67°C; NMR($CDCl_3$) δ 8.29(1H,d), 6.8(1H,d), 6.73(2H,d), 6.7(2H,d), 4.13(2H,q), 3.94(2H,t), 3.46(4H,t), 3.18(4H,t), 2.52(4H,m), 2.09(2H,m), 1.54(2H,m), 1.24(3H,t), 0.94(3H,t); m/e 412$(M+H)^+$.

The necessary starting material was prepared as follows:-

The product from Example 134, step (ii) (0.74g) in ethanol (25ml) and 1N hydrochloric acid (2.5ml) was hydrogenated at room temperature and atmospheric pressure over 10% palladium charcoal (0.15g) until uptake of hydrogen was complete. Catalyst was removed by filtration through diatomaceous earth and the filtrate evaporated. The residue was triturated with a mixture of ethyl acetate (25ml) and saturated sodium bicarbonate solution (25ml) and the insoluble solid was filtered and washed with water and ethyl acetate. The aqueous layer of the filtrate was extracted twice with dichloromethane and the combined organic extracts evaporated. The residue was combined with the ethyl acetate-insoluble material and treated with boiling ethanol (40ml), unsoluble material being removed by filtration. Evaportion of the filtrate gave 2-n-propyl-4-[4-(4-pyridyl)piperazin-1-yl]phenol (0.7g) as a solid NMR (d_6DMSO) δ 8.84-8.68(1H,m), 8.18(2H,d), 6.82(2H,m), 6.7(3H,m), 4.1(1H,m), 3.42(4H,t), 3.17(3H,s), 3.05(4H,t), 2.48(DMSO), 1.55(2H,m), 0.89(3H,t).

EXAMPLE 137: [2-n-propyl-4-[4-(4-pyridyl)piperazin-1-yl]]phenoxybutyric acid

In a similar manner to Example 26, but starting from the product of Example 136 was prepared the title compound in 64% yield; m.p. 207-209°C (from isopropanol); NMR(d_6DMSO) δ 8.18(2H,d), 6.7-6.92(5H,m), 3.91(2H,t), 3.45(4H,t), 3.10(4H,t), 2.5(DMSO), 2.4(2H,t), 1.91(2H,?), 1.54(2H,m), 0.9(3H,t) + isopropanol (0.69 mole %) at 3.79 and 1.04; m/e 384$(M+H)^+$. Calculated for $C_{22}H_{29}N_3O_3$. $0.7C_3H_7O$: C, 68.0; H, 8.2; N, 9.9. Found C, 68.1; H, 8.2; N, 9.9%.

EXAMPLE 138: Ethyl [2-methyl-4[4-(4-pyridyl)piperazin-1-yl]]phenoxybuyrate

In a similar manner to Example 25, but starting from 2-methyl-4[4-(4-pyridyl)piperazin-1-yl]phenol dihydrochloride was prepared the title compound in 29% yield as a gum; NMR($CDCl_3$ δ 8.3(2H,m), 6.45-6.35(5H,m), 4.14(2H,q), 3.87(2H,t), 3.14(4H,m), 2.53(2H,t), 2.21(3H,s), 2.11(2H,m), 1.24(3H,t); m/e 384$(M+H)^+$.

The necessary starting material was made as follows:-

i) Carbonyl diimidazole (5g) was added portionwise to a stirred suspension of N-benzyliminodiacetic acid (3.14g) in dry THF (50ml) at room temperature under argon. After 5 minutes, the mixture was heated at gentle reflux for 15 minutes and (4-amino-2-methyl)phenylbenzylether (3.0g) added and the mixture stirred at reflux for 17 hours. Solvent was evaporated and the residue was stirred with ethyl acetate (100ml) and water (150ml) for 1 1/2 hours. The solid was filtered, washed with water and dried to give [4-benzyl-2,6-diketopiperazin-1-yl]phenylbenzylether (4.7g); m.p. 118-126°C (dec); NMR ($CDCl_3$) δ 7.1-7.32(10H,m), 6.78(3H,s), 4.93(2H,s), 3.56(2H,s), 3.4(4H,s), 2.12(3H,s); m/e 373$(M+H)^+$.

(ii) To a solution of the product of step i) (2.9g) in dry THF (50ml) was added lithium aluminium hydride (0.6g) and the mixture heated at reflux for 1 1/2 hours. The mixture was allowed to cool and more (0.3g) lithium aluminium hydride added and reflux continued for a further 1 1/2 hours. The mixture was cooled and water (0.9ml) added followed by sodium hydroxide solution (1N, 3.6ml) and the mixture refluxed for 10 minutes. The solid was filtered and washed with THF. The filtrate and washings were evaporated and the residue purified by flash chromatography on silica gel, eluting with 5% ethyl acetate in dichloromethane increasing to 25% ethyl acetate. Thus was obtained [2-methyl-4-{4-(4-pyridyl)piperazin-1-yl}]phenylbenzyl ether as a solid (1g); m.p. 118-120°C; NMR($CDCl_3$) δ 7.2-7.5(10H,m), 6.82(1H,d), 6.80(1H,d), 6.7(1H,m), 5.01(2H,s), 3.1(4H,m), 2.53(3H,s); m/e 373$(M+H)^+$.

(iii) A suspension of the product of step ii) (1g) in 1,2-dichloroethane (25ml) was cooled in ice-water and treated with 1-chloroethylchloroformate (0.77g). The mixture was allowed to warm to room temperature, stirred for 30 minutes and heated at reflux for 30 minutes. Methanol (20ml) was added and the mixture refluxed again for 30 minutes and evaporated. The residue was triturated with ether and filtered. The solid was washed with ether and dried to give [2-methyl-[4-(4-pyridyl)piperazin-1-yl]]phenylbenzylether hydrochloride (0.95g); m.p. 195-198°C; NMR(d_6DMSO) δ9.44(2H,bs), 7.3-7.5(6H,m), 6.98(2H,m), 5.08(?,s), 4.98(4H,bs), 3.38(4H,d), 2.2(3H,s); m/e 281$(M+H)^+$.

(iv) A mixture of the product of step iii) (0.95g), 4-chloropyridine hydrochloride (0.46g) and triethylamine (0.615g) in water (10ml) was heated at 100°C for 3 hours. More 4-chloropyridine (0.34g) and triethylamine (0.3ml) was added and reflux continued for a further 3 hours. The solution was cooled and extracted with dichloromethane (2 x 15ml). The organic layer was evaporated and the residue was purified by flash chromatography on silica gel, eluting with 5% methanol in dichloromethane, containing 0.4% concentrated ammonia, to give [2-methyl-4-[4-(4-pyridyl)piperazin-1-yl]]phenylbenzyl ether (0.26g); as a solid; NMR(d_6-DMSO) δ 8.19(2H,d), 7.25-7.5(5H,m), 6.88(4H,m), 6.74(1H,m), 5.03(2H,s), 3.44(4H,bt), 3.1(4H,bt), 2.18(3H,s); m/e 360$(M+H)^+$.

(v) A solution of the product of step (iv) (0.52g) in ethanol (20ml) containing 2N hydrochloric acid (2ml) was stirred with 10% palladium/carbon (0.16g) under an atmosphere of hydrogen until hydrogen uptake was complete. The mixture was filtered and the filtrate evaporated. The residue was triturated with hot ethyl acetate and filtered to give, as a solid, 2-methyl-4-[4-(4-pyridyl)piperazin-1-yl]phenol dihydrochloride (0.55g); NMR(d_6-DMSO) δ 8.25(2H,d), 7.24(2H,d), 7.12(2H,bd), 6.8(1H,d), 4.02(4H,m), 3.46(4H,m), 2.1(3H,s); m/e 270$(M+H)^+$.

EXAMPLE 139: [2-methyl-4-[4-(4-pyridyl)piperazin-1-yl]]phenoxybutyric acid

In a similar manner to Example 26, but starting from the product of Example 138, the title compound was obtained in 80% yield as a solid, m.p. 261-262°C; NMR(d_6DMSO) δ 8.18(2H,d), 6.7-6.9(2H,m), 3.9(2H,t), 3.43(4H,bt), 3.1(4H,bt), 2.39(2H,t), 2.13(3H,s),1.72(2H,m); m/e 356$(M+H)^+$. Calculated for $C_{20}H_{25}N_3O_3$: C, 67.6; H, 7.1; N, 11.8. Found: C, 67.4; H, 6.9; N, 12.2%.

EXAMPLE 140: RS Methyl-2-t-butoxycarbonylamino-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyrate

In a similar manner to Example 25 but starting from RS methyl 4-bromo-2-t-butoxycarbonylaminobutyrate, the title compound was prepared in 65% yield as an oil; NMR($CDCl_3$) δ 8.31(2H,d), 6.9(4H,m), 6.71(2H,m), 5.3(1H,br), 4.5(1H,br.d), 4.01(2H,t), 3.77(3H,s), 3.5(4H,m), 3.21(4H,m), 2.3(2H,m), 1.46(9H,s); also signals at 8.03, 2.97 and 2.9(DMF) and 1.8(H_2O); m/e 471 $(M+H)^+$. Calculated for $C_{25}H_{34}N_4O_5$. 0.5DMF. 0.5H_2O: C, 61.7; H, 7.5; N, 12.2. Found: C, 61.8; H, 7.2; N, 11.9%.

The necessary starting material was made as follows:-

A solution of RS-methyl-N-butoxycarbonyl homoserinate (1.7g) and carbon tetrabromide (3.6g) in dichloromethane (20ml) was stirred at 5°C. Triphenylphosphine (3.77g) was added portionwise over 5 minutes. After 2 hours at room temperature the dark solution was evaporated and the residue triturated with ether/hexane (1/1, 30ml) until a solid was obtained. The solid was filtered and the filtrate evaporated. The residue was purified by flash chromatography, the product being eluted with 25% ethyl acetate/hexane to give RS methyl 4-bromo-2-butyloxycarbonylaminobutyrate (0.41g) as an oil; NMR($CDCl_3$) δ 5.16(1H,br), 4.45(1H,m), 3.8(3H,s), 3.45(2H,t), 2.52-2.11(2H,m), 1.48(9H,s); m/e 296$(M+H)^+$.

EXAMPLE 141: RS 2-t-butoxycarbonylamino-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyric acid

In a similar manner to Example 26, but starting from the compound of Example 140, there was obtained in 58% yield, the title compound as a solid; m.p. 198-207°C; NMR(d_6DMSO) δ 8.2(2H,d), 6.91(6H,m), 4.06(1H,m), 3.92(2H,t), 3.48(4H,t), 3.12(4H,t), 2.2-1.84(2H,m), 1.37(9H,s); m/e 457$(M+H)^+$. Calculated for $C_{24}H_{32}N_4O_5$. H_2O: C, 60.7; H, 7.2; N, 11.8. Found: C, 60.7; H, 7.2; N, 11.7%.

EXAMPLE 142: RS Methyl 2-amino-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybuyrate

The compound of Example 140 (0.96g) in TFA (10ml) was kept at room temperature for 2 hours. The solution was evaporated and the residue dissolved in water (15ml) and the solution basified with sodium carbonate. The mixture was extracted three times with dichloromethane. Evaporation of the combined extracts gave the title compound (0.56g); m.p. 125-127°C; NMR(d_6DMSO) δ 8.2(2H,d), 6.92(6H,m), 4.0(2H,m), 3.64(3H,s), 3.46(4H,t), 3.15(4H,t), 2.04(2H,m), 1.84(1H,m); m/e 371$(M+H)^+$. Calculated for $C_{20}H_{26}N_4O_3$. 0.75 H_2O: C, 62.5; H, 7.17; N, 14.6. Found: C, 62.8; H, 6.8; N, 14.3%.

EXAMPLE 143: 4-[2-[4-(4-pyridyl)piperazin-2-one-1-yl]acetyl]phenoxyacetic acid, sodium salt

The title compound of Example 35 (0.25g) in methanol (5ml) was treated with aqueous sodium hydroxide (1N, 0.65ml) and the mixture kept at room temperature for 6 hours. The solid thus formed was filtered and washed with methanol to give the title compound (0.18g); m.p. 317-318°C; NMR(d_6DMSO) δ 8.2(2H,d), 7.89(2H,d), 6.91(2H,d), 6.83(2H,d), 4.89(2H,s), 4.21(2H,s), 4.01(2H,s), 3.68(2H,m), 3.51(2H,m); m/e 392(M+H)$^+$; calculated for $C_{19}H_{18}N_3O_5Na$. $0.25H_2O$: C, 57.6; H, 4.6; N,10. Found: C, 57.2; H, 4.6; N, 10.4%.

EXAMPLE 144: Ethyl 4-[2-[4-(4-pyridyl)piperazin-2-one-1-yl]acetyl]phenoxyacetate

A crude sample of the product of Example 36 (3.4g) was treated with a solution, at 0°C, made by adding thionyl chloride (2.25g) dropwise to ethanol (45ml) with stirring at below 0°C. The mixture was stirred at room temperature for 2 hours, heated at gentle reflux for 2 1/2 hours, and evaporated. The residue was treated with water and adjusted to pH6 with aqueous sodium bicarbonate solution. The gum which precipitated was separated and the aqueous solution was adjusted to pH8 and extracted with dichloromethane (2 x 50ml). The combined extracts were washed with brine, dried and evaporated. The residue was purified by chromatography using a 10g. Mega Bond Elut silica gel column, eluting with 5% methanol/dichloromethane/0.5% triethylamine to give the title product as a solid (0.2g); m.p. 163-165°C; NMR($CDCl_3$) δ 8.34(2H,m), 7.97(2H,m), 6.98(2H,m), 6.63(2H,m), 4.89(2H,s), 4.7(2H,s), 4.29(2H,q), 4.1(2H,s), 3.7(2H,m), 3.6(2H,m), 1.31(3H,t); m/e 398(M+H)$^+$; calculated for $C_{21}H_{23}N_3O_5$: C, 63.5; M, 5.83; N, 10.6. Found: C, 61.5; H, 5.9; N, 10.5%.

EXAMPLE 145: Ethyl N 4-[2-(4-(4-pyridyl)piperazin-2-one-1-yl)acetyl]phenoxyacetylglycinate

The compound of Example 36 (0.37g) was stirred in DMF (10ml) with hydroxybenzotriazole (0.17g) and the mixture cooled in ice-water. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.14g) was added, followed by triethylamine (0.14ml) and the mixture stirred for 30 minutes. Glycine ethyl ester hydrochloride (0.15g) was now added, followed by triethylamine (0.28ml). After ten minutes stirring in the cold, the mixture was allowed to warm to room temperature, stirred for two days and evaporated. Water (10ml) was added to the residue and sodium bicarbonate added to pH6-7. The mixture was evaporated and the residue purified by chromatography on a Mega Bond Elut silica gel column (10g), eluting with 2% - 20% methanol/dichloromethane. The product was recrystallised from ethanol to give the title compound as a solid (36mg); m.p. 209-211°C; NMR(d_6DMSO) δ 8.55(1H,t), 8.2(2H,brd), 7.99(2H,m), 7.12(2H,m), 6.86(2H,d), 4.92(2H,s), 4.11(2H,q), 4.02(2H,s), 3.9(2H,d), 3.2(2H,m), 3.52(2H,m), 1.2(3H,t); m/e 455(M+H); calculated for $C_{23}H_{26}N_4O_6$: C, 60.8; H, 5.77; N, 12.3. Found: C, 60.6; H, 5.7; N, 12.5%.

EXAMPLE 146: Ethyl [2-nitro-4-[4-(4-pyridyl)piperazin-1-yl]]phenoxybutyrate

Sulphuric acid (98%, 2.5ml) was added slowly to the compound of Example 25 (1g) with stirring at room temperature. The solution was cooled to below 5°C and a mixture of nitric acid (0.18ml) and sulphuric acid (0.18ml) was added dropwise. The solution was stirred at below 10°C for 1 1/2 hours, poured onto ice and basified with ammonia solution to pH10. The mixture was extracted with ethyl acetate (2 x 50ml) and the extract washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel, the product being eluted with 5% - 10% methanol/dichloromethane to give the title product as an oil (0.18g); NMR($CDCl_3$) δ 8.32(2H,d), 7.41(1H,d), 7.14(1H,m), 7.04(1H,d), 6.77(2H,m), 4.17-4.14(4H,m), 3.51-3.28(8H,m), 2.57(2H,t), 2.14(2H,m), 1.28(3H,t), plus H_2O (1.87); m/e 415(M+H)$^+$; calculated for $C_{21}H_{26}N_4O_5$. $0.25H_2O$: C, 60.1; H,6.3; N, 13.1. Found: C, 60.2; H, 6.3; N 13.2%.

EXAMPLE 147: RS Methyl 2-n-butanesulphonylamino-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyrate

n-Butanesulphonylchloride (0.233g) was added to a stirred solution of the compound of Example 142 (0.5g) and triethylamine (0.15g) in dichloromethane (15ml) at room temperature. The solution was kept for 2 days and subjected to flash column chromatography on silica gel. The product was eluted with methanol/dichloromethane/0.88SG ammonia (7/93/0.7) v:v:v to give, after trituration with ether, the title compound in 58% yield as a solid; m.p. 124-125°c; NMR($CDCl_3$) δ 8.3(2H,d), 6.88(4H,q), 6.72(2H,m), 5.18(1H,br.d), 4.16(1H,br,q), 4.08(2H,t), 3.8(3H,s), 3.47(4H,m), 3.18(4H,m), 2.98(2H,m), 2.28(2H,m), 1.73(2H,m), 1.45-1.27(2H,m), 0.9(3H,t); m/e491(M+H)$^+$; calculated for $C_{24}H_{34}N_4O_5S$: C, 58.8; H, 7.0; N, 11.4. Found: C, 58.4; H, 7.0; N, 11.1%.

EXAMPLE 148: RS 2-n-butanesulphonylamino-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyric acid

In a similar manner to Example 26, but starting from the compound of Example 147, was prepared the title compound in 58% yield as a solid; m.p. 251-252°C; NMR(d_6DMSO) δ 8.18(2H,d), 7.3(1H,vbr), 6.9(6H,m), 3.97(2H,t), 3.9(1H,m), 3.45(4H,t), 3.11(4H,t), 2.9(2H,t), 2.12(1H,m), 1.92(1H,m), 1.58(2H,m), 0.81(3H,t); m/e 477$(M+H)^+$; calculated for $C_{23}H_{32}N_4O_5S$. 0.5 H_2O: C, 56.9; H, 6.8; N, 11.5. Found: C,57.0; H, 6.8; N, 11.3%.

EXAMPLE 149: RS 3-Benzyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyric acid

In a similar manner to Example 26, but starting from RS ethyl 3-benzyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyrate, was prepared the title compound in 65% yield as a solid; m.p. 205-206°C; NMR (d_6DMSO) δ 8.2(2H,d), 7.22(5H,m), 6.9(6H,m), 3.8(2H,d), 3.45(4H,m), 3.15(4H,m), 2.72(2H,m), 2.5-2.18(Me_2SO + 3H,m); m/e 432 $(M+H)^+$; calculated for $C_{26}H_{29}N_3O_3$. 0.25H_2O: C, 71.6; H, 6.8; N, 9.7. Found: C, 71.9; H, 6.8; N, 9.5%.

The necessary starting material was made as follows:-

(i) A solution of RS 3-benzylbutyrolactone (1.14g) in ethanol (20ml) was stirred at 5°C and gassed for 4 hours with a slow stream of hydrogen bromide. The solution was kept at 5°C for 20 hours and water (70ml) added followed by sodium carbonate to neutralise the acid. The mixture was extracted with ethyl acetate and the organic layer filterd through phase separating paper and evaporated to give ethyl 4-benzyl-3-bromobutyrate as an oil; NMR($CDCl_3$) δ 7.24(5H,m), 4.13(2H,q); 3.45(2H,m), 2.62(2H,d), 2.44(3H,m), 1.25(3H,t); m/e 285$(M+H)^+$.

(ii) In a similar manner to Example 25, but starting from the product of step (i) was prepared RS ethyl 3-benzyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybuyrate in 40% yield as an oil; NMR ($CDCl_3$) δ 8.34(2H,d), 7.29(5H,m), 6.9(4H,m), 6.72(2H,m), 5.13(2H,q), 3.85(2H,m), 3.5(4H,m), 3.3(4H,m), 2.9-2.38(5H,m), 1.26(3H,t); m/e 460$(M+H)^+$.

EXAMPLE 150: RS 3-phenyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyric acid

In a similar manner to Example 26, but starting from RS methyl 3-phenyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyrate, was prepared the title compound in 39% yield as a solid; m.p. 120-125°C; NMR(d_6DMSO) δ 8.18(2H,d), 7.32(5H,m), 7.25(2H,d), 6.87(6H,m), 4.04(2H,q), 3.45(5H,m), 3.11(4H,t), 2.71(2H,m); m/e 418$(M+H)^+$; calculated for $C_{25}H_{27}N_3O_3$. 0.25H_2O: C, 7.1; H,6.5; N,9.9. Found: C, 7.2; H, 6.5; N,9.8%.

The necessary starting material was made as follows:-

In a similar manner to Example 133 step (ii), but starting from RS ethyl 4-hydroxy-3-phenylbutyrate was made RS methyl-3-phenyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyrate in 10% yield as an oil; NMR(d_6DMSO +CD_3COOD) δ 8.23(2H,d), 7.3(5H,m), 7.17(2H,d), 6.95(2H,d), 6.83(2H,d), 4.06(2H,m), 3.77(4H,t), 3.55(3H,s), 3.51(1H,m), 3.17(4H,t), 2.83(2H,m); m/e 432$(M+H)^+$.

EXAMPLE 151: 3-[4-[4-(4-pyridyl)piperazin-1-yl]]-N-benzylbenzamidopropionic acid

In a similar manner to Example 31, but starting from methyl 3-[4-[4-(4-pyridyl)piperazin-1-yl]]-N-benzylbenzamido propionate was prepared the title compound in 72% yield as a solid; NMR (d_6DMSO) δ 2.5-2.6 (2H,m), 3.4-3.55 (6H,m), 3.75-3.85 (4H,m), 4.65 (2H,s), 6.95 (2H,d), 7.15 (2H,d), 7.2-7.45 (7H,m), 8.25 (2H,d); m/e 445 $(M+H)^+$; calculated for $C_{26}H_{28}N_4O_3$.0.5H_2O: C, 68.8; H, 6.3; N, 12.3. Found: C, 69.2; H, 5.8; N, 12.4%.

The necessary starting material was prepared as follows:-

(i) In a similar manner to Example 30, but using N-benzyl β-alanine methyl ester, was prepared methyl 3-[4-[4-(4-pyridyl)piperazin-1-yl]]-N-benzylbenzamido propionate in 34% yield as a solid; NMR ($CDCl_3$) δ 2.0-2.1 (2H,m), 2.6-2.7 (2H,t), 3.35-3.4 (4H,m), 3.45-3.55 (4H,m), 3.65 (3H,s), 4.65 (2H,s), 6.7 (2H,d), 6.85 (2H,d), 7.2-7.45 (7H,m), 8.2-8.35 (2H,m); m/e 459 $(M+H)^+$.

EXAMPLE 152: [2-propyl-4-[2-[4-(4-pyridyl)piperazin-2-one-1-yl]acetyl]]phenoxyacetic acid

Using the method of Example 131 but starting from methyl 2-^{n}propyl-phenoxyacetate, was prepared the title compound: NMR (d_6DMSO) δ 0.9 (3H,t), 1.55-1.7 (2H,m), 2.65 (2H,t), 3.45-3.55 (2H,m), 3.65-3.75 (2H,m), 4.05 (2H,s), 4.8 (2H,s), 4.9 (2H,s), 6.85 (2H,d), 6.9 (1H,d), 7.75-7.85 (2H,m), 8.2 (2H,d); m/e 412 $(M+H)^+$; calculated for $C_{22}H_{25}N_3O_5$.0.25H_2O: C, 63.5; H, 6.1; N, 10.1. Found: C, 63.5; H, 6.2; N, 9.9%.

The starting material was prepared as follows:-

(i) In a similar manner to Example 3 step (i), but starting from 2-allyl phenol, was prepared methyl 2-allyl-phenoxyacetate as an oil in 97% yield; NMR (d_6DMSO) δ 3.45 (2H,d), 3.7 (3H,s), 4.8 (2H,s), 5.0-5.1 (2H,m), 5.9-6.1 (1H,m), 6.85-6.95 (2H,m), 7.1-7.2 (2H,m); m/e 207 $(M+H)^+$.

(ii) The product of step (i)(5.86g) was dissolved in methanol (100ml) and a catalytic amount of 10% palladium on carbon was added. The mixture was hydrogenated at atmospheric pressure for 18 hours. The mixture was filtered and concentrated to an oil which was purified by flash column chromatography, eluting with ethyl acetate/hexane (10:90 v/v) to give methyl 2-^{n}propyl-phenoxyacetate (4.82g) as an oil; NMR (d_6DMSO) δ 1.4 (3H,t), 1.5-1.7 (2H,m), 2.6 (2H,t), 3.7 (3H,s), 4.8 (2H,s), 6.8-6.95 (2H,m), 7.1-7.2 (2H,m); m/e 208 $(M)^+$.

EXAMPLE 153: [2-methyl-4-[2-[4-(4-pyridyl)piperazin-2-one-1-yl]acetyl]]phenoxyacetic acid

In a similar manner to Example 131, but starting from methyl 2-methylphenoxyacetate , was prepared the title compound as a solid; NMR (d_6DMSO+CD_3COOD) δ 2.3 (3H,s), 3.6-3.7 (2H,m), 3.9-4.0 (2H,m), 4.35 (2H,s), 4.8 (2H,s), 4.95 (2H,s), 6.95 (1H,d), 7.15 (2H,d), 7.8-7.9 (2H,m), 8.25 (2H,d); m/e 384 $(M+H)^+$; calculated for $C_{20}H_{21}N_3O_5.1H_2O$: C, 59.8; H, 5.8; N, 10.0. Found: C, 59.3; H, 5.8: N, 10.1%.

EXAMPLE 154: Ethyl 4-[4-(4-pyridyl)piperazin-2-one-1-yl] phenoxybutyrate.

In a similar manner to that described in Example 25, but starting from 4-[4-(4-pyridyl)piperazin-2-one-1-yl] phenol, the title compound was prepared as a colourless solid (100 mg); NMR (d6 DMSO) : δ 1.2 (3H,t); 1.9-2.05 (2H,q); 2.45 (2H,t); 3.85 (2H,m); 3.95 (2H,m and 2H,t); 4.05 (2H,q); 4.4 (2H,s); 6.9 (2H,d); 7.15 (2H,d); 7.25 (2H,d); 8.25 (2H,d); m/e 384 (M+H)+.

The necessary starting material was prepared as follows:

(i) To a stirred suspension of 4-(4-pyridyl) piperazin-2-one (880 mg) in dimethyl formamide (20 ml) was added potassium hydride (1.0 ml of a 20% dispersion) and the mixture stirred for 0.5 hr, after which time was added copper (I) iodide (1.0 g). After 0.25 hr there was added 4-benzyloxybromobenzene (1.2 g) and the mixture stirred at 140°C in an argon atmosphere for 2 hr. The reaction mixture was diluted with water and brine and extracted with dichloromethane (3x40 ml); the combined extracts were washed with water and brine, dried (PS paper) and evaporated to give crude product as a pasty solid (2.0 g). This was purified by flash chromatography on silica, eluting with dichloromethane/methanol/conc. ammonia (97:2.5:0.5 v/v) to give 4-benzyloxy [4-(4-pyridyl)piperazin-2-one-1-yl]benzene as a colourless solid (1.1 g) NMR δ (d6 DMSO) :3.7-3.9 (4H,m); 4.1 (2H,s); 5.1 (2H,s); 6.85 (2H,d); 7.05 (2H,d); 7.25 (2H,d); 7.3-7.6 (5H,m); 8.2 (2H,d); m/e 360 (M+H)+.

(ii) To a solution of the product of step (i) (1.1 g) in a mixture of methanol (500 ml) and tetrahydrofuran (100 ml) was added 30% palladium-on-charcoal catalyst (300 mg) and the mixture stirred in an atmosphere of hydrogen at ambient temperature and pressure until all the starting material had been consumed. After removal of the catalyst by filtration, the solvent was evaporated in vacuo to give 4-[4-(4-pyridyl)piperazin-2-one-1-yl] phenol as a colourless solid, essentially one spot by tlc, which was used without further purification or characterisation.

EXAMPLE 155: 4-[4-(4-pyridyl)piperazin-2-one-1-yl] phenoxybutyric acid.

In a manner similar to that described in Example 26, but starting from the product of Example 154, the title compound was prepared as a colourless solid (95 mg); NMR (d6 DMSO) : δ 1.8-2.0 (2H,q); 2.35 (2H,t); 3.7-4.0 (4H,m + 2H,t); 4.3 (2H,s); 6.85 (2H,d); 7.05 (2H,d); 7.2 (2H,d); 8.15 (2H,d); m/e 356 (M+H)+.

EXAMPLE 156: [2-Nitro-4-[4-(4-pyridyl)piperazin-1-yl]]phenoxybutyric acid

In a similar manner to Example 26, but starting from the compound of Example 146, the title compound was obtained in 68% yield as a solid; m.p. 219-220°C; NMR(d_6DMSO) δ 8.2(2H,d), 7.4(1H,d), 7.27(2H,m), 6.98(2H,d), 4.08(2H,t), 3.23(4H,br.t), 2.36(2H,t); 1.69(2H,m); m/e 387$(M+H)^+$. Calculated for $C_{19}H_{22}N_4O_5$. H_2O: C, 56.4; H, 5.98; N, 13.9. Found: C, 56.7; H, 5.7; N, 13.9%.

EXAMPLE 157

Illustrative pharmaceutical dosage forms suitable for presenting the compounds of the invention for therapeutic or prophylactic use include the following, which may be obtained by conventional procedures well known in the art.

a)

Tablet I	mg/tablet
Active ingredient	1.0
Lactose Ph. Eur.	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v aqueous paste)	0.75
Magnesium stearate	1.0

b)

Tablet II	mg/tablet
Active ingredient	50
Lactose	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v aqueous paste)	2.25
Magnesium stearate	3.0

c)

Tablet III	mg/tablet
Active ingredient	100
Lactose	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v aqueous paste)	2.25
Magnesium stearate	3.0

d)

Capsule	mg/capsule
Active ingredient	10
Lactose Ph. Eur.	488.5
Magnesium stearate	1.5

(e)

Injection	mg/ml
Active ingredient (acid addition salt)	1.0
Sodium chloride	9.0
Purified water to 1.0ml	

Claims

1. RS 3-Methyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyric acid or a metabolically labile ester or amide thereof.

2. RS 3-Methyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyric acid or a pharmaceutically acceptable salt thereof.

3. RS 3-Methyl-4-[4-(4-pyridyl)piperazin-1-yl]phenoxybutyric acid.

4. A compound as defined in any one of claims 1 to 3 for use in medical therapy.

5. A pharmaceutically composition comprising a compound as defined in any one of claims 1 to 3 together with a pharmaceutically acceptable diluent or carrier.

6. Use of a compound, as defined in any one of claims 1 to 3 in the manufacture of a medicament for the prevention or treatment of a disease involving platelet aggregation.

7. Use of a compound, as defined in any one of claims 1 to 3 in the manufacture of a medicament for the prevention or treatment of a disease involving binding of fibrinogen to Glycoprotein IIb/IIIa.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 11 7909

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	CHEMICAL ABSTRACTS, vol. 98, no. 15, 11 April 1983 Columbus, Ohio, US; abstract no. 125889b, "Aromatic carboxylic acid derivatives" page 621; XP002046539 see 3-(dimethylamino)propyl ester of 4-(4-pyridinylamino)-benzoic acid (Registry number=85000-31-3) & JP 82 183 738 A (YAMANOUCHI PHARMACEUTICAL CO.) ---	1-7	C07D213/74 A61K31/44
A	EP 0 100 158 A (THE UPJOHN CO.) * page 7, line 16 - page 7, line 17 * -----	1-7	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	12 November 1997	De Jong, B

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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